

DIABETES MELLITUS

Principles and Treatment

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DIABETES MELLITUS

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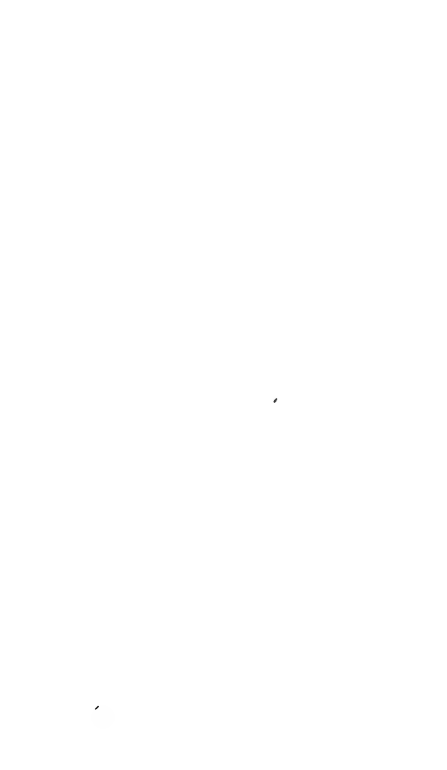
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Foreword

I appreciate the privilege of congratulating Dr. Duncan on his growing attainments in clinical medicine and on the authorship of the present work. The practical purpose of such a book is to teach the treatment of diabetes. Though there are other good books on this subject, a new one is not superfluous but is a needed addition to the weight of authority against wrong doctrines. The subject is controversial at a time when it should already have been clarified. Mortality and disability remain high when they should be negligible. Diabetes may be ranked as the worst treated of all diseases in relation to the knowledge and means available for its control. Granting the part played by ignorance and carelessness of patients, there is need of more warning against the widespread fatal errors of physicians.

The three main contributions of my early research can be claimed to have stood the test of time. First, the reduction of total calories and body weight diametrically contradicted the previous universal high calorie high fat tradition which aimed at maintaining the highest possible weight. The ideal of control was set up in cases previously classed as uncontrollable. ✓ For the first time diabetes was linked with total metabolism, beyond the narrow glucose metabolism. Second, the long familiar progressive loss of tolerance occurring in uncontrolled diabetes was elucidated by the experimental and clinical explanation of hydropic degeneration as a remarkable example of anatomic breakdown of an endocrine organ by functional over strain. This degeneration and loss of beta cells was shown to be prevented by the same diet plan which controlled diabetic symptoms. Immediately after the discovery of insulin, it was further shown that insulin administration cannot only prevent but also reverse this process so that the vacuolated cells regain granulation. On this evidence was based the first affirmation that diabetes is not spontaneously or inevitably progressive. Third, it was learned, first in dogs and then in young patients, that diabetes is still progressive when the blood sugar remains high, even without glycosuria. The resulting first advocacy of normal glycemia as the standard of control has been repeated in many of my publications since that time. This influence of hyperglycemia has lately been fully confirmed, particularly by Lukens' production of hydropic degeneration and permanent diabetes in normal cats by continued large glucose injections. The original postulate of connection between hyperglycemia and diabetic complications has theoretical and clinical support.

Immediately after the introduction of insulin the theory was proposed that treatment might consist in giving enough insulin to metabolize the requisite quantity of foodstuffs, without regard to urine or blood tests. The writers who have subsequently adopted and publicized this view are classifiable in three groups. First, a small number use a few years of observation as basis for the claim that full and continuous health is provided by insulin dosage which maintains normal weight and absence of acidosis, with complete disregard of diet restrictions or laboratory tests. A second group contradict the first group with long term observations showing that most or perhaps all patients thus treated ultimately fall victims of complications, but also that controlled diabetics have a similar statistical liability to the same complications, which therefore are regarded as inevitable and inherent in the disease rather than in the treatment. A third group occupy a twilight zone, being satisfied with various degrees of control of sugar in urine and blood, often fearing hypoglycemia more than hyperglycemia and considering normal glycemia as risky or detrimental in some cases. In actual practice, the result of prevalent teachings has been to include the majority of physicians in this country and throughout the world in this third group.

My own attitude toward this literature may likewise be stated in three parts. (a) While the appearance of gross complications may be deferred for twenty or more years, they ultimately occur in most and probably all uncontrolled diabetic cases. Occasionally there is opportunity to see the onset of a complication after prolonged hyperglycemia with little or no

hantle blood sugar made normal. Since

insulin daily, such a degree of prolonged deficiency of a vital hormone should not be expected to be harmless. (b) I hazard the opinion that statistics proving similar incidence of complications in controlled and uncontrolled diabetes are nonexistent. In other words, the cases listed as controlled by these writers have not been controlled in any proper sense of the word. This criticism is not mere hair-splitting and does not refer to brief or slight accidents of control. The occurrence of a typical complication is *ipso facto* proof of lax treatment in the sense of gross and prolonged elevations or fluctuations of blood sugar, with the specific tissue malnutrition which they signify. (c) This opinion is derived from thirty-five years of clinical experience, which has comprised numerous complications occurring in seemingly well nourished patients, without acidosis and with excellent subjective feelings under various degrees of lax treatment, but not a single example in well controlled cases either with good nutrition under insulin or with severe undernutrition in the time before insulin. It should furthermore be emphasized that, apart from a few exceptionally labile cases, properly managed control with insulin does not

burden patients with serious hardships or with the supposed danger of hypoglycemia

This statement applies not to the ordinary senile events occurring at natural ages, but to all typical diabetic complications, particularly the premature and excessive arteriosclerosis. It comprises the uniform prevention of these lesions in early or youthful cases, the frequent but not invariable arrest of processes already active and the apparent halting of arteriosclerosis even in an advanced stage, so that no such case has gone on to gangrene and (barring one traumatic accident) no patient who had previously lost one leg has ever developed gangrene in the other. Therefore for many years I have promised every cooperative patient a full lifetime of health, and I have had a standing challenge to family physicians and the various consultants who see these patients to report a single occurrence of any of the familiar complications, and nobody has yet shown an exception. Such a sweeping claim was at first qualified by recognition of the frequency of peripheral vascular disease, sometimes entailing gangrene, among the nondiabetic population, and the consequent likelihood of this nonspecific process in occasional diabetics, so that the absence of any such examples to date has seemed noteworthy. As mentioned, the guide in diabetes has been solely metabolic normality as judged by the most delicate known index, namely the blood sugar. The guidance has disregarded incidental or secondary manifestations in the confidence, for example, that normal lipid metabolism is assured by control of the general disorder rather than by limitation of dietary cholesterol.

Briefly, then, the therapeutic principle in diabetes is the same as in any other disease. The patient being abnormal, the physician's duty is to make him normal. The means are available in diet and insulin. It is tragic that the great discovery of insulin should have been used for carelessness instead of thoroughness of treatment. Dr. Duncan's book will place the issue on permanent record for future judgment of responsibility on one side for a mistaken dogma of preventability, or on the other side for literally millions of preventable tragedies of blindness, other disabilities and premature deaths world wide throughout the past quarter century.

Dr. Duncan has distinguished several eras in diabetic treatment, but there should be the utmost awakening to the revolutionary epoch which lies ahead, in which the ideals will receive practical application so as to abolish all complications. Perhaps the carefully ordered life of the diabetic may even set the example for longevity and freedom from arterial and organic degenerations beyond the present average among the general population.

FREDERICK M. ALLEN

Preface

The objectives in preparing this volume have been twofold, first, to bring together and correlate up to date principles in the understanding of and in the treatment for diabetes mellitus and, second, to deal with this disease and its complications in such a manner that physicians and students may find herein a practicable and simplified outline of therapy

In fulfilling these objectives it has been necessary to cover quite a wide range, touching on nearly every specialty in Internal Medicine, as well as making excursions into the fields of Physiology, Physiological Chemistry, Pathology, Surgery, and Dietetics We have avoided as much as possible *controversial issues and multiplicity of theories and practices*, by giving most emphasis to known pathologic changes, to known phenomena influencing therapy and by outlining in considerable detail the practical measures, including the simplified Food Exchange System recently adopted by the American Diabetes Association, which have proved most useful in our experience

No apology is offered for frequent repetition of important concepts It is by this process that those physicians and students who do not see large numbers of diabetic patients will quickly grasp the relative importance of the facts presented

Illustrations have been used freely, especially in depicting the pathologic changes associated with diabetes Detailed considerations are given to the many facets of therapy and a considerable section of the book has been devoted to the complications—chronic and acute—of diabetes

All of the references needed to serve the practical purposes of our objectives are included This, of course, is by no means a complete bibliography of the subject

Reasonable calculations indicate that there are between one and one half and two million diabetic patients in this country Also, approximately 25 per cent of the total population have diabetic relatives These facts indicate the enormity of the overall problem presented by diabetes Our responsibilities embrace the early detection of the diabetes, adequate treatment a continuous educational program, the encouragement of research into the hidden mysteries of the disturbed physiology as encountered in diabetes and the prompt but wise clinical application of every advance achieved

I wish to express my sincere appreciation to my colleagues for their co-operation in this enterprise I am especially grateful to Dr A Reynolds

Crane, Pathologist to the Pennsylvania Hospital, for his constructive criticism and for several of the illustrations depicting pathologic changes characteristic of diabetes, to Dr John B Flick for his interest and efforts in behalf of our surgical patients, to Drs John B Alexander and Henry Russell for assistance in compiling data, and to Drs Frederick M Allen, Samuel Soskin and Joseph H Barach, Mr H H Marks and the U S Department of Public Health for permission to reproduce illustrations and other data from their publications

For painstaking and efficient secretarial service we are especially indebted to Miss Loretta M Stieber, and to Mrs Dorothea E Duncan for her very able assistance with the manuscript

To those who collaborated with me in the writing of this book I am especially indebted not only for this immediate enterprise but for the years of interest and work which they have devoted to making the lot for the diabetic patients a better one.

To the Dietary and Nursing Departments and to the many workers whose names do not appear but upon whose teachings and writings we have drawn in the fulfillment of our objectives, I am grateful

To Dr Frederick M Allen, with whom I spent two happy and profitable years, I owe much and I am especially grateful to him for his introduction to this volume

The cooperation and happy relations with the W B Saunders Company have lightened greatly the labor of preparing this work in its final form

GARFIELD G DUNCAN

April, 1951

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CHAPTER I

Diabetes Mellitus

I DEFINITION

Diabetes mellitus is a chronic disease manifested by multiple disturbances in the metabolic processes of the body. It is the result of a decrease in the production of endogenous insulin, or of other changes which increase, to a marked degree, the need for insulin. These features singly or in combination produce a relative or absolute insufficiency of insulin and account for the far reaching pathologic and clinical changes characteristic of this disease. Following promptly upon the development of hypoinsulinism, disturbances in the metabolism of carbohydrate become apparent. The concentration of sugar in the blood increases above normal—*hyperglycemia*—and sugar appears in the urine—*glycosuria*. The frequent passing of large volumes of urine—*polyuria*—ensues. Dehydration, and the simultaneous loss of minerals, and loss of flesh follow in spite of excessive hunger—*polyphagia*—and thirst—*polydipsia*. As the loss of sugar increases protein is drawn upon in an attempt to replace sugar, to supply energy and, as a result, a negative nitrogen balance ensues, and wasting of muscle becomes prominent. Also the catabolism or breaking down of fat is speeded up in direct proportion to the reduction of carbohydrate utilization. As the metabolism of fat is accelerated a point is reached when the acetone bodies are produced in quantities beyond the capacity of the tissues to utilize them and the excretion of acetone in the urine follows.

Unless these processes are favorably influenced by treatment they tend to progress until the full capacity of the kidneys to excrete acetone bodies is reached. It is at this stage that the retention of acetone bodies in the blood becomes detectable in increasing amounts. Unchecked, these processes, with great latitude in the ranges of progressiveness, will lead to a fatal outcome.

Stetten¹ in investigating biologic processes by the isotope technic, has shown that under normal conditions a considerable portion of the body fat is broken down and re-synthesized daily and that insulin is quantitatively more involved in the synthesis of fat from carbohydrate than it is in the synthesis of glycogen. He found that about ten times as much goes into the formation of fat as into the formation of glycogen. In

diabetic, both of these processes—fat and glycogen production—are interfered with to a great degree and sugar, normally used in fat and glycogen production, is not utilized but accumulates in the blood and is excreted. It is clear why the untreated diabetic patients lose weight so rapidly and why they gain so readily when insulin is supplied. It is apparent that diabetes disturbs not only carbohydrate but protein, fat and total food and tissue metabolism as well—a fact that Allen has postulated for many years.

The disturbances in metabolism in diabetes are remarkably accelerated and increased in degree by *acute infections* and *toxemias*. It will be observed in the pages which follow that facilities now at hand have reduced almost to the disappearing point the risks which these complications formerly held. Fifty years ago, Joslin² reports, 63.8 per cent of the patients died of diabetic coma, whereas now a death due to this complication is rare (1.9 per cent).

Formerly, attention was focused on the changes recorded above and their immediate ramifications. The picture has changed. Diabetes, by lending itself well to control with diet and insulin, has been subdued and life has been remarkably prolonged. As the acute difficulties yielded to therapy and longevity was improved chronic changes became more and more evident until now *degenerative diseases* have replaced *acute complications* as the most common causes of death in the diabetic population. We refer especially to premature arteriosclerosis and the hazards it presents. Prominent among these is insufficiency of the coronary circulation. Occlusive processes involving one of the coronary arteries have become the most common causes of death of adult diabetic patients. Arterial sclerosis and retinal hemorrhages, intercapillary glomerulosclerosis and the diabetic neuropathies, also degenerative in nature, have assumed positions of increasing importance in the diabetic population. Peripheral vascular disease continues to be a great hazard. The great reduction of the mortality from diabetic gangrene does not mean that the underlying cause has been conquered. Quite the contrary, peripheral vascular disease in diabetics is more prevalent than ever. This is not surprising with the average age at death now being sixty-four instead of forty-four years (1898-1941).³ Methods of treating the complications which immediately threaten life have improved to such a degree that a false sense of security is understandable, but nothing should detract attention from the underlying menace of arteriosclerosis and from attempts to solve the problems it poses.

The understanding of *uncomplicated diabetes* and the individualized considerations necessary, the early recognition of and treatment for *acute complications*—ketosis, infections, thyrotoxicosis, etc.—and the acceptance of the challenge which the *degenerative diseases* present are essential if maximum benefit is to accrue for these patients.

of anterior pituitary or adrenal hormone a more severe form of the disease develops and large amounts of insulin are usually needed to preserve good health. Also, the temporary diabetes resulting from injections of adreno corticotrophic hormone (ACTH) is relatively resistant to insulin.

Following removal of the pancreas from the dog the blood sugar rises above normal, the glycogen stores, particularly those in the liver, become depleted and sugar is lost in the urine in large amounts (Table 1). As the diabetes remains unchecked nitrogen excretion in the urine increases, indicating a sacrifice of protein in an attempt to meet the deficiencies incurred by the reduced metabolism of carbohydrate. The synthesis of fat is reduced drastically and the catabolism of fat is increased. The latter process becomes intensified and eventually to a degree when more acetone bodies are produced in the breakdown of fat than can be oxidized. As a result acetone appears in the urine and, barring relief from treatment, acetone bodies eventually accumulate in the blood, giving rise to ketosis.

TABLE I
SOME EFFECTS FOLLOWING REMOVAL OF PANCREAS

Hyperglycemia
Glycosuria
Reduced glycogen—liver, muscle and skin
Reduction of Respiratory Quotient
Relative constancy between nitrogen and glucose excretion
Increased nitrogen excretion in the urine
Acetonuria
Dehydration
Demineralization
Ketosis
Death—usually within 4 to 14 days unless treated

which, in the advanced stages, causes coma and death following a progression of the derangements mentioned above and the dehydration, hemoconcentration, loss of base, and peripheral vascular collapse which are associated with them in the final stages.

Pituitary Gland and Diabetes. The anterior pituitary gland is the major coordinator of the endocrine glands. As such, it has widespread influence on carbohydrate metabolism. One of the uncommon causes of diabetes is an hormonal imbalance associated with basophilic adenomas of the pituitary gland. Housay* (1936) observed that the removal of the pancreas from an animal deprived of its pituitary gland caused a more attenuated diabetes than was the case when a normal dog was subjected to pancreatectomy. Evans and Housay caused a transitory diabetes in dogs by injecting crude extracts of the anterior pituitary gland. Young,⁷ by pyramiding the dosage of such extracts, produced, in adult dogs, a permanent diabetes. Destruction of the islets of Langerhans occurred as a result of the administration of pituitary extracts. Haist⁸ prevented the effect of

of Addison's disease and diabetes. The effects of increased adrenal cortical hormones are illustrated in cases of Cushing's disease.

Experimental studies and the clinical evaluation of cases of disturbed adrenocorticotrophic hormone have aided in the understanding of the part played by the adrenal cortex in diabetic and nondiabetic individuals. The adrenal glands influence greatly the availability of glucose and its utilization in the tissues. Both of these features are of importance in clinical diabetes.

The Thyroid Gland and Diabetes. Clinically, the thyroid gland affects carbohydrate metabolism in direct proportion to the metabolic rate over which it maintains a most important control. In thyrotoxicosis carbohydrate is absorbed more rapidly than normal—a feature which may lead to faulty interpretation of glucose tolerance curves (see p. 79). Diabetes tends to be intensified by excessive thyroid therapy or thyrotoxicosis.

TABLE 3

ALTERATIONS IN FUNCTION OF THE THYROID GLAND AND DIABETES

	THYROTOXICOSIS	CONTROL OF THYROTOXICOSIS
Diabetes	Aggravated	Ameliorated
Blood sugar	Readily elevated	More stable
Glycosuria	Aggravated	Tends to be corrected
"	"	Depressed
"	"	Normal or slightly decreased
"	"	Normal or slightly decreased
"	"	Normal
"	"	Normal
"	"	Reduced
"	"	Prolonged

and the opposite in the case with the development of hypothyroidism (Table 3). However, the thyroid hormone is not a diabetogenic hormone in the same sense as are the pituitary gland and the adrenocortico steroids. It affects carbohydrate metabolism and hence diabetes through its influence on the rate of tissue metabolism. Thyroidectomy does not alleviate a total diabetes (Lukens and Dohan¹²).

Evolution in Therapy for Diabetes. The construction of the bases upon which the present therapy for diabetes rests has entailed much research which has been rewarded at times with sudden great advances with interim periods during which a slower but never completely static evolutionary change took place.

Dr. Elliott P. Joslin has emphasized these different phases of progress by naming the respective eras or epochs after the physicians responsible for the new developments in the understanding of and therapy for diabetes. The eras so depicted are as follows:

Naunyn era	1898 to 1914
Allen era	1914 to 1922
Banting era	1922 to 1936
Hagedorn era	1937 to 1943
Best era	1944 to date

The Naunyn Era (1898-1914)

Naunyn was the foremost authority on diabetes of his time. He influenced greatly the advancement of clinical and experimental knowledge of this disease. He was well aware of the hereditary basis of diabetes and was, until 1886, the champion of a strict carbohydrate free diet. Later, he supported a more rational treatment reckoning the diet on the tolerance for carbohydrate and caloric requirements of each patient. To Naunyn's pupils we owe much of the early understanding of clinical acidosis. Naunyn introduced the term "acidosis."

Naunyn's plan of treatment for diabetes was that of a gradual withdrawal of the carbohydrate, the increase of the diet after glycosuria had subsided to 35 to 40 calories per kilogram of body weight and about 125 gm. of protein with the carbohydrate allowance being established below the amount which would cause glycosuria, occasional fast days were employed when glycosuria was persistent. However, prolonged undernutrition or the loss of more than 2 kilograms of weight was avoided. Diets high in protein and fat content were the rule. The administration of large doses of sodium bicarbonate in cases of acidosis, brisk exercise for the patient having mild diabetes and much less physical activity when the disorder was of a severe degree were advocated.

Naunyn had a strong conviction that diabetes should be energetically treated as soon as the diagnosis was made. With this concept present day authorities on the subject are agreed.

The Allen Era (1914-1922)

Allen contributed greatly to the knowledge of the pathology of diabetes. His proofs of the effects of changes in total metabolism on diabetes are of outstanding clinical importance. The principles of undernutrition as a therapeutic measure in the treatment for diabetes are just as true today as when they were introduced in 1914. Fortunately they need not be as rigorously employed as it was necessary to do in the pre-insulin days. Allen emphasized the value of a reduction in the total caloric intake and employed this measure to such a degree that one or two fast days were included per week with submaintenance diets on the remaining days when the diabetes could not be controlled by less strict means. In this manner many patients were kept alive who would otherwise have been lost before insulin became available. Allen showed that loss of weight from uncon-

History of Diabetes

Diabetes mellitus has presented clinician and investigator with the problems of aberrations of metabolism, the wrestling with which has increased understanding of metabolism in general and to a degree much more advanced than would have been so if the demand for solution had not been ever present in the form of serious clinical complications. The history of diabetes as presented by Allen¹ relates that in the *Ancient Period* "the passing of frequent and large quantities of urine" was recorded in the papyrus Ebers, an Egyptian medical journal already old in the time of Moses (Saundby). "Polyuria without pain but with emaciation and danger" was recorded in reference to diabetes by Celsus (30 B C-50 A D). The Ionic Greek name *diabetes*, meaning "to run through a siphon," was given by Aretaeus (30-90 A D), who also wrote of the "progressiveness of diabetes" and of the "fatal prognosis" associated with this disease. Diabetes was described as a "disease of thirst" by Tchang Tchangking (200 A D) who observed a patient, suffering from this disease, drink ten quarts of water per day with a relative degree of polyuria. "Excessive appetite" was recorded as a symptom of diabetes by Chinese writers about 600 A D. The "sweetness of the urine" of diabetic patients was first mentioned by Ayur Veda Susruta (Chunder Rose). Ants were observed to flock around the patients' urine and "weakness, emaciation, polyuria and carbuncles" were associated with diabetes.

Diabetic gangrene was described as such by Avicenna (980-1037 A D). *Furunculosis* and *tuberculosis* were recognized as characteristic complications of diabetes in the fifteenth century. Crystals were formed on the evaporation of the urine of a diabetic patient by Paracelsus (1493-1541), who mistook them for "salt," and *lipemia* was first associated with diabetes by Helmont (1578-1644).

In the *Second or Diagnostic Period* Willis (died 1675) observed the urine of the diabetic patient to be "wonderfully sweet as if imbued with honey or sugar." Willis was the first to advocate a carbohydrate or undernutrition "cure." The hereditary nature of diabetes was made clear by Morton (died 1693), and Dobson in 1775 grasped the fact for the first time that the sweetness of the urine was due to sugar. Disease of the pan-

creas was first described as occurring in a patient dying of diabetes by Cawley (1713). There were multiple pancreatic calculi and much destruction of pancreatic tissue. The adjective *mellitus* was added to diabetes by Cullen (1709-1790) to distinguish the disorder from diabetes insipidus. Francis Home, on adding yeast to urine of the diabetic patient, learned that the sweetness disappeared and at the same time established the fermentability of the sugar.

In the *Third Period or Period of Empiric Treatment*, Rollo (1796) restricted the diet to animal food and a few green vegetables and he was the first to note and record the significance of *diabetic cataracts*. The "odor of decaying apples" was noted on the breath of a young diabetic patient by Marshall (1790). The sugar in the urine was identified as glucose by Chevreul (1815) and Gregory (1825) described the differences between diabetes mellitus and diabetes insipidus. Prout advocated "restriction of protein" in the treatment for diabetes. He introduced washed bran as an adjunct in diet therapy and he described coma as a typical and end result of diabetes.

In the *Modern or Experimental Period* Gregory demonstrated a fermentable sugar in the blood of diabetic patients, Trommer in 1811 and Fehling in 1850 introduced qualitative tests for sugar in the urine, Claude Bernard (1813-1891) founded the theory of sugar formation from glycogen and postulated that increased blood sugar levels were due to overproduction of sugar by the liver, Mialhe (1845) recommended the use of alkali in the treatment for diabetes. Bouchardat (1806-1886) substituted alcohol and fat for carbohydrate, he individualized his patients' needs, advocated small diets with an occasional day of fasting and introduced thrice cooked vegetables and gluten bread. He observed advantages of physical exercise and advocated the daily testing of the urine for sugar. Acetone was recovered from the urine of a patient in diabetic coma by Petters in 1837 and Kussmaul in 1874 described the type of breathing, which still bears his name observed in patients in diabetic coma. Severely restricted diets, 'fast days', physical exercise and insistence of complete freedom from glycosuria were standards used by Cantani (1837-1893). That all diabetes was pancreatic in origin was hypothesized by Baumer. Ehrlich noted glycolytic degeneration of renal tubules in diabetes and Kutz (1845-1893) identified oxaluric acid in the urine of diabetic patients. He also observed that exercise helped patients having mild diabetes but that the opposite was true if the diabetes were severe.

Islet cell formations in the pancreas were discovered by Langerhans in 1869. Diabetes following pancreatectomy in a dog was observed by von Mering and Minkowski (1889) who established the doctrine of the internal secretion of the pancreas and it was Minkowski who discovered the low CO_2 combining power of the blood in diabetic coma. Naunyn introduced the term *acidosis*. He recognized clinical renal glycosuria and he employed

diets with low carbohydrate, low protein and high fat contents in the management of diabetes. *Hydropic degeneration of the islets of Langerhans* in diabetics was reported by Weichselbaum and Stangle but it was Opie, in 1901, and Ssobolew who proposed the theory that diabetes was "due to alterations in these islets." Roulston and Woodyatt, Newburgh and Marsh, Petren, Wilder and Shaffer, employed diets with high fat content but it was with Allen's introduction of *undernutrition* as a *therapeutic measure in treating diabetics* that the first really great advance in therapy was made.

Important advances including and subsequent to the introduction of Allen's undernutrition regimen will be dealt with in considerable detail throughout this book but for the sake of completeness the more important advances in the understanding of and treatment for diabetes are listed here.

Joslin and others confirmed the benefits of Allen's undernutrition therapy which rapidly became the treatment of choice. Allen presented the hypothesis that diabetes was "a disorder of total metabolism and not of carbohydrate metabolism alone."

Then *insulin* was discovered in 1921 by Banting and Best. This discovery dwarfed in importance all others, especially as they dealt with severe and complicated diabetes. A trend to more liberal calories and carbohydrate promptly ensued and gradually as the effects of insulin and other modifications of therapy which insulin permitted, the entire outlook for the diabetic patient became so altered that it is difficult in 1951 to envision that only a few years ago semi-starvation was the price patients with severe diabetes had to pay to remain alive. Even this price was of no avail in cases of children and many of the emaciated adult diabetic patients.

Removal of the pituitary gland from a dog increased the animal's sensitivity to insulin (Houssay and Magenta, 1924) but this hypersensitivity was diminished by treatment with pituitary preparations (Houssay and Potick, 1929). The severity of diabetes was decreased by hypophysectomy (Houssay and Biasotti, 1930) and a transitory diabetes was provoked by injecting a normal dog with anterior pituitary extract (Houssay, Biasotti, and Riets, Evans, Bauman and Marini, 1932) and diabetes was made more severe by injecting anterior pituitary gland extracts (Houssay and Biasotti, Houssay, 1936). Diabetes was attenuated by the removal of the adrenal cortex of depancreatized cats (Long and Lukens, 1936). Then, in 1937, Young experimentally produced permanent diabetes by injecting intraperitoneally increasing amounts of crude extract of the anterior pituitary gland. Experimental diabetes was made more severe by giving large doses of cortin in depancreatized adrenalectomized dogs (Lukens and Dohan, 1938).

Protamine insulin was discovered by Hagedorn (1936) and the improved combination *protamine zinc insulin* was made available as a result

of the investigations of Scott and Fisher (1936). The latter provided a stable product of slow and prolonged action.

Restoration of hydrologically degenerated pancreatic islets by adequate insulin therapy (Copp and Barclay, 1923, Lukens and Dohan, 1910) and the protection from the diabetogenic effect of injections of pituitary extract by administering large doses of insulin, by a starvation regimen or by a high fat diet (Hart, Campbell and Best, 1910), added to our knowledge of this complex subject.

The selective destruction of the beta or insulin producing cells of the islets of Langerhans by the intravenous injection of alloxan (Jacobs, 1937, Dunn and McLetchie, 1943, Bailey and Bailey, 1943, Goldner and Gomori, 1943) presented a new approach to the study of diabetes and possibly to its etiology. Also, the administration of glutathione, a normal component of the body, protects against the diabetogenic effects of alloxan. Alloxan can be derived from uric acid. The development of hyperglycemia and glycosuria following injections of ACTH is reversed by administering glutathione (Conn, 1949).

Hyperglycemia, in rats, maintained by intraperitoneal injections of glucose, has been shown to produce diabetes and it has been demonstrated that control of the diabetes in the early stages reverses the pathologic processes and produces a cure (Dohan and Lukens, 1947).

Tagging nutritional components of a diet with radioactive labels and observing their behavior and fate is affording a means of making an infinitely more profound chemical analysis of disturbed values in diabetes than has been possible heretofore (Stetten, 1943). Hyperglycemia and glycosuria have been produced in rabbits by intraperitoneal injections of uric acid after reducing blood glutathione concentrations to a low level by means of a diet deficient in cystine and methionine (Lazarow, 1946, and Griffiths, 1943). The two principles of this process—glutathione and uric acid—are normal constituents of the human body. One is tempted to speculate!

Hormonal imbalance and its management in pregnant diabetic patients (Smith, Smith, and Hurwitz, 1944, White, 1943) and the importance of hypokalemia immediately following therapy for diabetic coma (Guest, 1942, Holker, 1946, Nadler *et al.*, 1943) are among the significant advances in reducing the mortality rate from these complications. The elaboration of the value of electrocardiography in detecting hypokalemia during therapy for diabetic coma by Bellet *et al.* (1950) also is of great clinical significance. The far reaching benefits derived from sulfonamide and antibiotic therapies should be included in a listing of historical landmarks dealing with progress for the diabetic patient.

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1940, and that an increase of 18 per cent could be expected by 1950, during which time the expected increase in the total population would be only 9 per cent. It has been estimated that more than 4,350,000 of the present population of the United States would eventually become diabetic. It is highly probable that the total number of diabetics has been underestimated. The high incidence of diabetes found in the course of Selective Service examinations indicates a higher frequency of this disease among the younger age group than was formerly considered.³

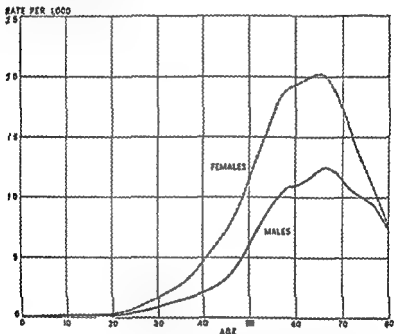


Fig. 1 Diabetes onset rates per 1000 (Chances of becoming diabetic within the year of age) United States, 1935-1936.⁴

Age and Sex. The National Health Survey (1935-36) revealed that the incidence of diabetes increased steadily until the seventh decade of life in both sexes. There has been no significant change so far in the twentieth century in the age at onset of the diabetes in any of the decades of life (Table 1). The peak incidence for the onset of diabetes for both sexes occurs between fifty and seventy years of life, as indicated in Figure 1.

The constantly increasing life expectancy of diabetic patients on the one hand, with no significant change on the other hand, in the age at onset of the diabetes, is a prominent factor in the increasing incidence of diabetes in the older age groups.

Diabetes occurs more frequently in the female than in the male. Marks⁵

CHAPTER III

Incidence of Diabetes

Total Number of Cases. Diabetes is more prevalent than ever before and the incidence of the disease, though not accurately known, is steadily increasing. There are more than one million known diabetics in the United States in 1951, and newly identified cases are currently amounting to 55,000 annually.¹ The increasing incidence of recognized cases is due, in part, to a newly awakened public interest and action arising from the educational activities of the American Diabetes Association and its subsidiary branches, and partly to the broadening scope of regular check up and insurance examinations. Absolute increases in the incidence of diabetes are attributable to the greater numbers of our population in the older

TABLE 4
AGE AT ONSET OF DIABETES (JOSLIN)

DECADES	PER CENT APPEARING IN EACH DECADE 1936-1938	
	Males (1265 patients)	Females (1622 patients)
1	6.7	4.6
2	9.0	6.2
3	8.6	6.2
4	13.1	11.0
5	19.8	21.0
6	22.1	20.1
7	16.2	18.1
8	4.3	4.1
9	0.2	0.1
	100	100

age groups, to the improvement in treatment which permits diabetics a span of life closely approaching that of the normal, and to the increasing number of young diabetics who marry and have children who are more likely to develop diabetes than are children of normal parents.

Spiegelman and Marks² estimated, on the basis of a National Health Survey in a house to house canvas involving 200,000 families and 2,600,000 persons, that there were 500,000 diabetics in the United States in

1910, and that an increase of 18 per cent could be expected by 1950, during which time the expected increase in the total population would be only 9 per cent. It has been estimated that more than 4,350,000 of the present population of the United States would eventually become diabetic. It is highly probable that the total number of diabetics has been underestimated. The high incidence of diabetes found in the course of Selective Service examinations indicates a higher frequency of the disease among the younger age group than was formerly considered.

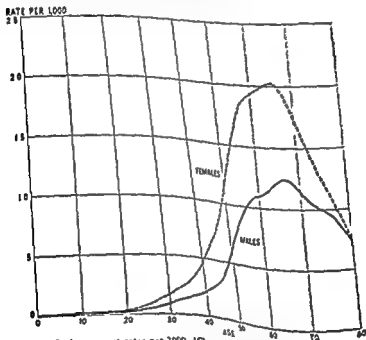


Fig 1 Diabetes on-set rates per 1000 (Charts of known diabetes within the year of age) (Lancet, 1950, 1951)

Age and Sex. The National Health Survey (1955-56) revealed that the incidence of diabetes increased steadily with the seventh decade of life in both sexes. There has been no significant change so far in the twentieth century in the age at onset of the diabetes in any of the decades of life (Table 1). The peak incidence for the onset of diabetes for both sexes occurs between fifty and seventy years of life as indicated in Figure 1.

The constantly increasing life expectancy of diabetic patients on the one hand, with no significant change on the other in the age at onset of the diabetes, is a prominent factor in the increasing incidence of diabetes in the older age groups.

Diabetes occurs more frequently in the female sex than in the male sex.

estimates that 21 per cent of the male population of 1946 will become diabetic and that 38 per cent, or nearly twice as many, of the female population will develop this disease. In the National Health Survey,⁴ 9182 diabetics were encountered and 61.2 per cent of these were female. Women live longer and are less active physically than men and are more prone to become obese between forty and seventy years of age than are the men.

The chances of eventually becoming diabetic, by age and sex, are presented in Table 5.

The incidence of diabetes is higher in married than in single women⁵ over forty five years of age and especially higher in women who have borne children. Married women who have had children weigh more than single women. This increased body weight undoubtedly influences the in-

TABLE 5
CHANCES PER 1000 OF EVENTUALLY BECOMING DIABETIC BY SEX AND AGE
UNITED STATES 1935-1936 (MARKS)¹

AGE	MALES	FEMALES
Under 15	22.1	41.5
15-19	22.4	42.0
20-24	22.6	42.3
25-29	22.8	42.6
30-34	22.8	42.6
35-39	22.7	42.2
40-44	22.4	41.3
45-49	21.9	39.4
50-54	20.7	36.2
55-59	18.1	30.7
60-64	14.8	23.8
65-69	11.3	16.6
70-74	7.7	10.0
75-79	4.6	5.2
80-84	2.0	2.0
85-89	0.4	0.4

cidence of diabetes unfavorably. The security enjoyed by the average married woman over forty five years of age influences the likelihood of gaining in body weight and hence a greater likelihood of developing diabetes. There is an increasing incidence of diabetes in women over forty five years of age out of all proportion to that observed in the male population. The seriousness of the diabetic problem in women over forty five years of age is depicted in Figure 1. The increase in the mortality rate of this group over male diabetics of the same age is striking (Fig. 2).

Occupation. Diabetes is more prevalent in urban than in rural communities. This is true also of the mortality from diabetes, which is between 60 and 70 per cent higher in the former area. The disease occurs more frequently among the employing and professional groups and among those engaged in selling and serving food and drink.

The mortality rates as applied to the various occupations illustrate well the beneficial effects of occupations calling for ample physical activity and at the same time highlight the hazards of ownership and other occupations in which there is relatively little need for much physical activity. Hired help on farms do more physical work than the farm owner and are less likely to develop diabetes than their employers. Mechanization of labor will tend to increase rather than decrease the incidence of this disease and the complications which arise as a result of it.

Race. Members of the Jewish race, particularly women, and especially those over forty years of age, are more prone to develop diabetes than the population as a whole. Jews comprise approximately 3.5 per cent of the population of the United States and yet among 5000 new diabetic patients Joslin found 810 or 16.2 per cent to be Jews. It is conservatively estimated that diabetes is one and one-half times as common among the older Jews as it is in the average population. This applies in all countries although probably is most clearly shown in Greater New York (Jewish Commercial Survey, 1931).

This racial predisposition has been attributed to persecution which prevented Jews from owning or tilling land, forcing them into more sedentary occupations. Probably the most important cause is the inbreeding of this race, with occupation and obesity as precipitating rather than essential causes. The effects of occupation, prosperity and well being in predisposing to diabetes are exemplified in the higher incidence of diabetes in the Irish in the United States than occurs in the same race living in Ireland. Diabetes is common among the Teutonic races and uncommon among the Slavs and Latins. The Negro race was formerly, and erroneously, believed to be relatively free from diabetes. With the improvement of social standing and prosperity with larger numbers of Negroes doing less physical work, obesity and diabetes have increased with greater frequency in the colored than in the white race. Approximately 35 per cent of the patients attending the Out Patient Diabetic Clinic at the Pennsylvania Hospital are of the Negro race.

Diabetes is relatively infrequent among the Chinese and Japanese and severe forms of the disease are unusual in these races.

Estimates have been made that there were 300,000 diabetics in Germany in 1933, 150,000 to 200,000 in the United Kingdom in 1932.

Diabetes rates at best are inaccurate. In some countries the incidence is calculated most reliably by using the mortality rates. The lack of uniformity in recording the causes (actual and contributory) of death makes most figures speculative.

Mortality. Lack of uniformity in reporting causes of death detracts from the value of these vital statistics. Often, the diabetes has not been recorded on the death certificate if the patient also had cancer. This is but an illustration of how the record of the death of a diabetic may fail to

reach statistics dealing with diabetes. Approximately two thirds only of the death certificates of diabetics contain a record of the diabetes. Hence the recorded deaths of 3559 diabetic patients in Pennsylvania in 1919 may be one third lower than the actual experience. The new death certificate form^a should aid in correcting statistics dealing with diabetic patients in the future.

The death rates from diabetes are higher in the United States than in any other country. The census reveals that 36,311 persons died from diabetes in 1913, 31,948 in 1914, 35,160 in 1915, 31,731 in 1916, and 37,515 in 1917. These figures represent 27.1, 26.4, 26.6, 24.8 and 26.2 per 100,000, respectively.

TABLE 6

DEATH RATES FOR THE TEN LEADING CAUSES UNITED STATES 1915-17*

(Exclusive of stillbirths and of deaths among armed forces overseas. Rates per 100,000 estimated mid year population excluding armed forces overseas)

CAUSE OF DEATH	1917	1916	1915
ALL CAUSES	1 007.8	997.6	1 061.8
Diseases of the heart	321.2	306.1	321.4
Cancer and other malignant tumors	132.1	130.1	131.4
Intracranial lesions of vascular origin	91.4	89.8	97.8
Nephritis	56.0	58.4	66.7
	46.6	46.2	51.4
	43.1	41.5	51.8
	33.5	36.4	40.1
	28.6	28.5	23.9
	26.2	21.8	26.6
..	22.8	23.9	21.3

* After Vital Statistics—Special Reports National Summaries 31 (No. 3) 22 (May 9) 1919

Diabetes ranks ninth in the list of major causes of death, 1915-1917 (Table 6), in contrast to twenty seventh place in 1900. It caused in 1913, three times as many deaths as tuberculosis in white women over forty five years of age.⁶ With improved therapy for tuberculosis and pneumonia, diabetes is certain shortly to be the seventh major cause of death in all age groups and in both sexes.

Provisional data indicate an increase in the death rate of 6 per cent for the country as a whole for 1919 over that of 1918.⁷

The mortality rate of diabetes increases steadily until the eighth decade of life. The older age groups have absorbed the increased mortality rates from diabetes. This naturally follows the reduced rates in diabetics under fifty years of age, the aging of the population—diabetic and general—and the more frequent diagnosis of diabetes in elderly individuals. The average age at death of diabetic policy holders of the Metropolitan Life Insurance Company had increased from 51.5 years in 1911 to 61.5 years in 1915.

Sex exerts influences in the mortality rates as well as the incidence of diabetes. Over thirty four years of age the death rate in females exceeds increasingly that of males as shown in Figure 2, until in the later decades it is nearly twice that recorded for the males. This is in more or less degree, the experience in other countries as well as in the United States and Canada.

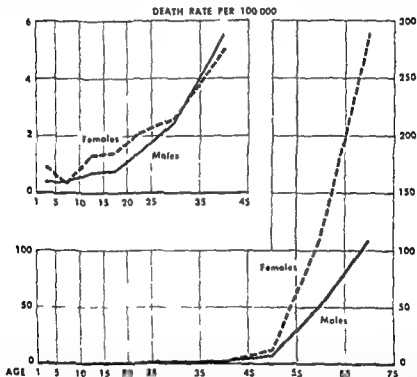


Fig. 2. Diabetes Death Rates by Sex and Age Among White Persons, Metropolitan Life Insurance Company Industrial Department, 1946-1948 indicate (1) a low rate in childhood and young adult life (2) a rapid acceleration of the death rate after forty five years of age in both sexes and (3) the increasing excess of rates for females over that of the males after forty five years of age, reaching nearly 2½ times that for males between the ages of sixty five and seventy four.

(After Spiegelman M., and Marks H. H. *Am J Pul Health*, 36:26, 1946)

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TABLE 6

DEATH RATES FOR THE TEN LEADING CAUSES, UNITED STATES, 1915-47*

(Exclusive of stillbirths and of deaths among armed forces overseas. Rates per 100,000 estimated mid year population excluding armed forces overseas)

CAUSE OF DEATH	1947	1946	1945
ALL CAUSES	1 007.8	997.6	1 061.8
Diseases of the heart	321.2	306.8	321.4
Cancer and other malignant tumors	132.4	130.2	131.4
Intracranial lesions of vascular origin	91.4	89.8	97.8
Nephritis	56.0	53.4	66.7
Accidents (excluding motor vehicle accidents)	46.6	46.2	51.4
Pneumonia (all forms) and influenza	43.1	41.5	51.8
Tuberculosis (all forms)	33.5	36.4	40.1
Premature birth	28.6	28.5	23.9
Diabetes mellitus	26.2	24.8	26.6
Motor vehicle accidents	22.8	23.9	21.3

* After Vital Statistics—Special Reports National Summaries 31 (No. 3) 22 (May 9) 1949

Diabetes ranks ninth in the list of major causes of death, 1915-1947 (Table 6), in contrast to twenty-seventh place in 1900. It caused, in 1943, three times as many deaths as tuberculosis in white women over forty-five years of age.⁶ With improved therapy for tuberculosis and pneumonia diabetes is certain, shortly, to be the seventh major cause of death in all age groups and in both sexes.

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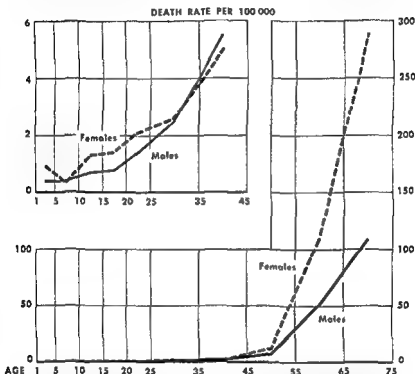


Fig 2 Diabetes Death Rates by Sex and Age Among White Persons, Metropolitan Life Insurance Company, Industrial Department, 1916-1918, indicate (1) a low rate in childhood and young adult life, (2) a rapid acceleration of the death rate after forty five years of age in both sexes and (3) the increasing excess of rates for females over that of the males after forty five years of age, reaching nearly 2½ times that for males between the ages of sixty five and seventy four

(After Spiegelman M., and Marks H II Am J Pub Health 36:26, 1946)

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CHAPTER IV

Etiology of Diabetes

INTRODUCTION

The exact cause of clinical diabetes appearing spontaneously is unknown. The circumstances which surround the incidence of this disease in certain groups, e.g., diabetic families," obese persons, and the methods of producing diabetes experimentally, incriminate *heredity, obesity, damage to or loss of the insulin producing beta cells of the islets of Langerhans, hormonal imbalances* and other features inadequately explained. Notable among the last mentioned are the extreme degrees of insulin resistance.

Whatever factor or factors culminate in clinical diabetes, it is generally agreed that this disorder represents a disproportion between insulin need and insulin production and that this does not necessarily mean an insulin production below normal. It is known that the demand for insulin often exceeds the amount necessary to control adequately the diabetes which results from a total pancreatectomy. The totally depancreatized adult human develops a daily insulin requirement between 30 and 50 units.¹ This is in contrast to the large number of diabetic patients needing more than 50 units daily and especially those highly resistant to insulin who may require several hundreds of units, or more, daily. In alluding to the low insulin need of the depancreatized man we are aware that the number of such cases is exceedingly small, that the duration of life in the depancreatized state is relatively short, and that the nutritional status and the total metabolism are likely to be grossly disturbed. Pancreatectomy seriously disturbs nutrition by reducing the absorption of fat and protein and this is doubtless a big factor. In addition there is evidence that the removal of the pancreas with its alpha cells removes the source of a hyperglycemic factor. Hence, if this is true, it explains why the totally depancreatized human needs less insulin than a diabetic who retains the potential possibility of producing an anti insulin factor.

PREDISPOSING FACTORS

Heredity. The predisposition to diabetes by heredity is established. Superimposed upon an inherited inadequacy may be other precipitating or deciding factors notably obesity and much less frequently, endocrine dis-

turbances. Over 50 per cent of diabetic children have a family history of diabetes. White and Pincus* to whom we owe the clear cut understanding of the hereditary basis of diabetes present as evidence of this conclusion (1) the almost simultaneous development of diabetes in identical twins, (2) the higher incidence of the disease among blood relatives of diabetics, and (3) the behavior of the incidence of diabetes in accordance with Mendelian patterns. The Mendelian pattern depicts diabetes as carrying recessive characteristics. It is predictable that, (1) if both parents have diabetes all of their immediate offspring will have diabetes if they live long enough, (2) if only one parent has diabetes and the other parent is nondiabetic but has a diabetic father or mother, the chances are even that the non-diabetic parent is a carrier. A diabetic child of such a union would establish the nondiabetic parent as a carrier and that other children of this union stand a 50 per cent chance of developing diabetes. The chances of the children of this union developing diabetes are less than 50 per cent if the nondiabetic parent who may or may not be a carrier, has a diabetic brother or sister. If the nondiabetic parent has a distant relative with diabetes it is unlikely, but possible that the children will develop diabetes. (3) if neither parent has diabetes but each had a parent who had diabetes the chances are 1 in 4 for the development of diabetes in their children, if a child of carrier parents develops diabetes the chances are 1 in 4 that the brothers and sisters will develop diabetes also, if a diabetic or diabetic carrier marries a nondiabetic from a nondiabetic family none of the immediate offspring will develop diabetes. The breeding out of diabetes falls within the realm of possibility. To achieve this a consistent union of descendants of diabetic patients with those of nondiabetic families for several generations would be essential.

Granted an hereditary basis for diabetes exists, the onset of the disease is modified by body weight, age, endocrine disturbances, occupation, infections and, possibly, by race.

Obesity It is known as a result of Allen's observations, which have been amply confirmed, that diabetes is ameliorated when the body weight is reduced by decreasing the caloric intake. Also, the need for insulin increases remarkably with increasing body weight. The obese diabetic is relatively resistant to insulin. Nevertheless the obese diabetics, excepting those who have become obese by virtue of insulin plus a diet high in calories have mild diabetes. Yet, if insulin is administered to such patients relatively large amounts are necessary to make much impression on the

units of insulin daily to correct a moderate hyperglycemia and yet when this large dosage of insulin is suddenly and completely withdrawn no acute manifestations result and indeed the blood sugar concentrations increase

but little (See Table 13, p 93) This is in contrast to the *underweight* diabetic patient who may be taking less than 100 units of insulin daily and who is sensitive to insulin, the sudden withdrawal of which would expose him to the risk of prompt and serious consequences From these clinical observations it is logical to conclude that *pre diabetic obese* persons maintain a normal blood sugar and delay or prevent the onset of diabetes by producing enormous amounts of endogenous insulin and that this increased demand leads eventually to an exhaustion of the islet cells and the onset of clinical diabetes in individuals also predisposed by heredity to this disease It appears unlikely that the explanation for these changes at this stage is to be found in a hormonal imbalance, although the initial onset of the metabolic abnormality may be so related Alterations in the total metabolism by a combination of reducing weight and a low caloric intake on one hand and an *increasing total body mass* and increasing weight on the other, offer a working clinical hypothesis which is merely a continued application of the principles laid down by Allen and which are applicable to the majority of adult diabetic patients when first seen by a physician for treatment

Seventy to 80 per cent of diabetic patients are, or give a history of having been, overweight, and yet in the reception room of a physician specializing in the treatment for diabetes there is no such predominance of the obese Many have lost weight prior to seeking help but have lost it in an undesirable manner, namely, from the progressiveness of the diabetes This results from loss of sugar and, at times, ketone bodies with no concomitant reduction in caloric intake Under these circumstances the insulin producing islet cells are subjected to a sustained stimulation to produce *maximum amounts of insulin* and the diabetes becomes intensified in direct proportion to the ensuing islet cell exhaustion

Race. All comprehensive studies of the racial incidence of diabetes show a higher frequency of this disease among Jewish males and females White and Pincus² contrast a positive family history of diabetes in 30.3 per cent of Jewish males with 23 per cent in all males, and 29.1 per cent in Jewish females with 26.5 per cent in all females Inbreeding tends by virtue of the predisposition by heredity to intensify this increased incidence of diabetes among Jews

Endocrine Factors Clinically, the co existence of diabetes with other endocrine disorders is not frequent However, its occurrence in patients with hyperfunctioning of the anterior pituitary and adrenal glands, as seen in Cushing's syndrome, and experimental studies leave no doubt concerning endocrine antagonisms Over 25 per cent of acromegalic patients develop diabetes

It is in the experimental field that most of our knowledge concerning disturbed harmony between the endocrine glands in diabetes has been

gained Permanent diabetes has been produced (1) by removal of the pancreas (Von Mering and Minkowski),³ (2) by partial pancreatectomy—removing nine tenths of the gland—with subsequent overfeeding (Allen),⁴ (3) by the injection of saline extracts of the anterior pituitary gland (Young),⁵ (4) by the injection of alloxan⁶ (5) by intraperitoneal injection of glucose in the cat (Dohan and Lukens)⁷ Transient diabetes has been produced by injecting uric acid into glutathione deficient rabbits.⁸

Allen proved the necessity of removing nine tenths of the pancreas before diabetes could be produced by overfeeding and his co workers, Copp and Barclay,⁹ found that control of the diabetes prevented progressive degeneration of the islets of Langerhans and that hydropically degenerated cells in the diabetic animal could be rescued by controlling the diabetes with insulin and diet Lukens and co workers¹⁰ who confirmed these observations believe that it is the hyperglycemia that is responsible for the degenerative changes in the islets These studies are of great importance to the physician treating diabetes They provide experimental support to the clinical conclusions of authorities in this field that control of the diabetes is an important force in preventing progression of degenerative changes in diabetic patients

When Young⁵ produced permanent diabetes in dogs by injecting increasing amounts of an extract of the anterior pituitary gland he observed that a reduction in the number of islets resulted Haist¹¹ found a great reduction in the insulin content of the pancreas of animals made diabetic by Young's method Similarly, in the pancreas of the human diabetic Scott and Fisher¹² found that the average amount of insulin in the normal pancreas was 1.7 units per gram in contrast to the average of 0.4 units per gram in the diabetic A decreased production of insulin by the pancreas of the diabetic could explain the presence of diabetes in some cases But in the large number of patients who require much more insulin to control the diabetes than is produced by the normal pancreas, as judged by the insulin need of the depancreatized human other factors must be at work There may be profligate waste of insulin in the body in a manner not known This may be due to neutralization of insulin blocking of enzymatic processes destruction or inhibition by insulin antagonists or proteolytic enzymes any one or any combination of which may conceivably influence the onset of diabetes

Miscellaneous Factors Age The fact that the onset of diabetes is most frequent between the ages of forty five and sixty five has been presented as evidence in favor of a pituitary influence at an age when in women the concentration of the anterior pituitary hormone in the blood is high The onset of diabetes at puberty though with a much lower peak is considered to be due in part at least, to the increased production of the same hormone The onset of diabetes does not occur in direct rela-

but little (See Table 13, p 93) This is in contrast to the underweight diabetetic patient who may be taking less than 100 units of insulin daily and who is sensitive to insulin, the sudden withdrawal of which would expose him to the risk of prompt and serious consequences From these clinical observations it is logical to conclude that pre diabetic obese persons maintain a normal blood sugar and delay or prevent the onset of diabetes by producing enormous amounts of endogenous insulin and that thus increased demand leads eventually to an exhaustion of the islet cells and the onset of clinical diabetes in individuals also predisposed by heredity to this disease It appears unlikely that the explanation for these changes at this stage is to be found in a hormonal imbalance, although the initial onset of the metabolic abnormality may be so related Alterations in the total metabolism by a combination of reducing weight and a low caloric intake on one hand and an increasing total body mass and increasing weight on the other, offer a working clinical hypothesis which is merely a continued application of the principles laid down by Allen and which are applicable to the majority of adult diabetic patients when first seen by a physician for treatment

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tion to aging, the frequency of new cases decreasing steadily after the mid sixties

The tendency to become overweight in the forties and fifties with the resulting increase in total metabolism has a definite bearing on the increased incidence of new cases of diabetes at this age. The decreasing total metabolism in later life has the opposite effect, probably accounting for the decline in new cases after fifty five years of age.

Infections Infections play little, if any, part in causing diabetes. Most infections, especially pyogenic infections, causing leukocytosis and fever, intensify the severity of diabetes while they persist. It is not surprising therefore, that diabetes, undetected at other times, may be recognized for the first time during the course of such infections. Viral infections and infections which do not cause leukocytosis, notably tuberculosis, have much less effect than pyogenic infections in increasing the severity of the diabetes during the course of the complication. In fact, occasionally the progressive emaciation attending tuberculous infections has been noted to decrease instead of increase the severity of the diabetes. It would appear that the decreasing total metabolism in such cases has a great insulin sparing effect which more than neutralizes the effect of the infection, and a decreasing insulin need ensues. Infections involving the biliary and pancreatic tracts may conceivably cause secondary islet cell destruction with an ensuing diabetes. If this does occur it must be rare. The disturbing effects which infections exert on existing diabetes is dealt with in the chapter on complications.

Arteriosclerosis Arteriosclerosis *per se* is not a cause of diabetes. If it were, the incidence of this disease would not be decreasing during the phase of life in which arteriosclerosis is on the increase.

Trauma Direct and extensive injury to the pancreas could conceivably cause diabetes, although this is extremely unlikely. Injury to other parts of the body will not affect the carbohydrate function except through inactivity, fever, and changes in body weight that might result.

Destruction of the Pancreas Progressive destruction of the islets by infiltrative lesions, tumors, by the fibrotic changes incident to hemochromatosis, or secondary to pancreatic calculi, will cause diabetes. Such cases have no relation to the clinical problems of diabetes in general.

Endocrines Hyperfunction of the pituitary and adrenal glands causes diabetes as seen in Cushing's syndrome, but the place of such glandular disorders in causing clinical diabetes as it is generally seen despite the fact that these disorders lend themselves well to laboratory study, is not clearly established. Hyperfunction of the thyroid intensifies diabetes probably in a manner similar to obesity, namely, in increasing the total metabolism. Cure of the thyrotoxicosis, like reduction of the obesity, usually ameliorates the diabetes.

are they rare

A third group—the middle aged overweight patients—provide, not infrequently, candidates whose diabetes is pushed back and off the stage of detection by a reduction in weight through the agency of a reduced caloric intake. The onset of the diabetes in these patients is not acute, the disappearance, but not a cure, of the diabetes is due to the reduced total body mass and hence the total metabolism by a means which spares islet cell function, and to the reduced need for insulin when the synthesis of fat from carbohydrate is reduced. This is in contrast to the deleterious effect that accompanies the loss of weight due to the activity of the diabetes, features of which are hyperglycemia and the excretion of large quantities of sugar and acetone in the urine.

The benefits of the reduction in weight by virtue of a restricted caloric intake form the basis of Allen's¹ undernutrition treatment. Benefits from undernutrition are obtainable in the insulin era, in properly selected cases (see p. 106) as we have previously demonstrated.^{4, 5, 6} Newburgh⁷ also has found support for the undernutrition regimen in the treatment of obese diabetic patients. The diabetes is not cured by the reduction in weight by undernutrition means. In spite of normal responses to glucose tolerance tests for varying periods a return of the former degree of obesity is invariably accompanied by evidences of diabetes. Also, without a gain in weight diabetes puts in an appearance during the course of acute infections, notably pyogenic infections. It would appear that in these cases the benefit is due to the reduction in total metabolism and that the supply of insulin is insufficient for the obese state is adequate when the total body mass is reduced. An analogy used in teaching patients is that a small furnace—in this case the pancreas—is incapable of heating a big factory or plant but if the size of the plant is reduced to conform with the size of the furnace satisfactory results ensue.

It is clear that if the eradication of all signs of diabetes is to be achieved in the individual case, the diagnosis in the young diabetics must be made in the very early days of the disease and vigorous and adequate therapy must be employed, and that in the older overweight patients a suitable reduction in weight should be achieved in an appropriate manner and the ground thus gained must be held.

Prospects of Acquiring Complications. Diabetics are just as prone to develop most of the common diseases as are members of the general population. They are more likely than their normal counterparts to be victims of certain acute disorders notably furuncles, carbuncles, tuberculosis and malnutrition, if their diabetes is uncontrolled.

The prognosis will depend upon three integrated features (a) the

Prognosis

The prognosis or outlook for the diabetic patient should be evaluated from (a) the standpoint of a *possible cure* of the diabetes and the advantages of *good control* of the disorder in its chronic form, (b) the prospects of *acquiring complications* with the influences that play for or against their development, and (c) *life expectancy*.

Possibilities of Curing Diabetes. A cure cannot be promised in any case of diabetes. Yet, those who have seen many of these patients have encountered occasionally one whose diabetes apparently disappears following appropriate treatment. At least, the diabetes is no longer detectable using the usual diagnostic measures. This is an unusual occurrence and one that should not be looked upon as a cure until many years pass with normal responses to annual diagnostic tests. One of us has had a special interest in two children followed for many years after all detectable signs of an acute diabetes had disappeared. In both cases the onset was acute. In one it was possible to record the onset of symptoms to a certain afternoon. It is highly probable that in such cases acute reversible processes are taking place in the islets of Langerhans and that prompt and adequate treatment rescues a number of "knocked out" functioning units sufficient to produce insulin in amounts adequate to erase evidences of diabetes.

Allen and his associates¹ have demonstrated that, in animals, islet cells in a state of hydropic degeneration can be redeemed by relieving the functional overstrain on these cells by restoring to and maintaining the blood sugar at normal concentrations by means of diet and insulin. Lukens and Dohan² have confirmed these observations.

Illustrative of the transient disappearance of diabetes is the case of J. E., aged thirty-eight years, height 6 feet, weight 180 pounds, who while en route to the hospital was found unconscious and anuric. Treated with insulin and glucose (venous) sugar values of 100 mg per 100 cc and values after taking 100 gm of glucose were one half hour 137 mg, one hour 88 mg, two hours 96 mg, and three hours 93 mg. Subsequent tests showed a marked improvement was necessary for him to secure a pension. The fasting blood (venous) sugar value was 119 mg per 100 cc and values after taking 100 gm of glucose were one half hour 137 mg, one hour 88 mg, two hours 96 mg, and three hours 93 mg. Subsequent tests

of therapy vary greatly. Those we have set, and our aims, are outlined in Chapter VIII. Life insurance policies are issued to selected diabetic patients who are known to be conservative and cooperative.

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change in the character of the diabetes as a result of the complications, (b) the management of the complication and (c) the proper evaluation of and the institution of appropriate measures to combat the influence which diabetes has upon the complication and *vice versa*. These features are dealt with in Chapters \V to \VII. Actually, when suitable treatment is available the outlook for the diabetic suffering from most of the acute complications is excellent. It is as good as in the nondiabetic. Diabetic coma, the specific acute complication of diabetes, has become an uncommon cause of death—less than 2 per cent of diabetic deaths in well equipped hospitals.

The complications which cause most concern are those characterized by *chronic degenerative changes*—vascular disease, notably disease of the coronary arteries and of the arteries of the extremities, diabetic retinitis, intercapillary glomerulosclerosis and the diabetic neuropathies.

Disease of the coronary arteries is the most common cause of death in diabetics at the Pennsylvania Hospital, accounting for 18 deaths in 514 diabetic patients admitted to the public wards because of acute complications. Malignant tumors was the second most common cause of death, occurring in 9 of the 514 patients, and cerebral vascular accidents the third in frequency, accounting for 8 deaths. Intercapillary glomerulosclerosis is a menace of increasing proportions (see p. 197). In fact, it was the most common cause of death in patients whose diabetes developed in childhood and who had survived fifteen or more years,⁸ whereas deaths from diabetic gangrene have declined precipitously since the advent of extensive antibiotic therapy.

Evidence is steadily accumulating that the likelihood of the diabetic acquiring any or all of these distressing chronic complications increases with the duration of the diabetes and the increase bears a direct relation to poor control of the diabetes.

Life Expectancy. The normal life expectancy for white males and females in the United States, as calculated in 1946, was 65.1 and 70.3 years, respectively. Statistics issued by the Metropolitan Life Insurance Company⁹ indicate that the life expectancy for white male diabetics is 62.12 and for white females, 66.20 years. The proximity of the life expectancy for diabetic patients to the normal expectancy has progressed rapidly since the discovery of insulin. Actually, many diabetic patients outlive the normal life expectancy.

The child diabetic lived but a short time—a scant two years—in the pre-insulin era. Contrast this with Joslin's¹⁰ statistics of today—of 2659 diabetic children treated since 1898, 2235 are alive¹.

The prognosis for the intelligent and cooperative diabetic patient is excellent if the diabetes is identified early and treated diligently by a physician who has interest and training in this field of metabolism. Standards

the injection. The degree of effect and duration of action are reduced or intensified by decreasing or increasing the doses, respectively. There is no need to give insulin intravenously except in doing insulin tolerance tests and part of the initial dose in the treatment of a patient in diabetic coma is given in this manner (see p. 231). The effect of insulin on the blood sugar level may be masked by frequent and liberal intake of food, particularly carbohydrate and, as would be expected, the effect is more apparent when no food is given.

Insulin is a protein and as such is destroyed by gastric juices, hence it is ineffective when given by mouth. The hypoglycemic effect which follows the injection of insulin is due to an increased rate of withdrawal of sugar from the blood by body tissues. Insulin permits increased deposits of glycogen in skeletal muscles, providing hypoglycemic levels are prevented. Glycogen is also deposited in greater quantities in the liver of the diabetic patient when the diabetes is controlled by treatment with insulin. Insulin administered to normal animals causes a reduction in the hepatic glycogen. In the diabetic insulin also exerts an antiketogenic effect: it increases the respiratory quotient, it reduces the concentration of serum inorganic phosphate and serum potassium, and it inhibits protein catabolism when administered to the diabetic patient who is excreting large amounts of sugar and ketones.

Lack of insulin results in a reduction in utilization and in a shortage of carbohydrate in the peripheral tissues. Insulin promotes utilization of glucose—complete oxidation, or deposition as glycogen, or synthesis to fat—by effecting a control over an enzyme, hexokinase (Corti). This enzyme exerts a catalytic action on the metabolism of glucose with adenosine triphosphate (ATP) to produce glucose 6 phosphate—a product available for oxidation, or for conversion to glycogen, or for synthesis to fat—a basic phosphorylation process. These processes studied *in vitro* were found to result when insulin completely released the inhibition of the hexokinase by pituitary and adrenal cortex fractions.

"The fall in the blood sugar level is a direct reflection of the influence of insulin on the basic phosphorylation, in so far as it causes a greater rate of removal of sugar from the blood (Soskin).³ Insulin also participates in reactions in the tricarboxylic cycle⁴—in the specific synthesis of phosphate in the metabolism of pyruvate to carbon dioxide and in accelerating the conversion of acetate to fatty acids. Though investigators have gained headway in solving the problems surrounding the action of insulin much is still not clear.

The fact that insulin is not essential for glycogen to be restored to skeletal muscles following physical exercise is of considerable clinical significance. The rate but not the extent of restoration is reduced if insulin is absent (Lukens).⁵ In the insulin treated patients the withdrawal of sugar from the blood for the replenishment of glycogen in muscles is an impor-

Discovery of Insulin. 'On the 27th of July, 1921, we had a depancreatized dog and we decided to begin treatment. A duct tied dog was chloroformed and the degenerated residue of pancreas was removed. It was chopped into small pieces in a chilled mortar and frozen in brine. The mass was ground up and about 100 cc of saline added. Of this extract 5 cc were administered intravenously into the depancreatized dog. Samples of blood were taken at half hour intervals and showed that the blood sugar had fallen from 0.20 to 0.11 per cent in two hours. The clinical condition of the dog was remarkably improved' (Banting).¹ An effective blood sugar lowering agent was thus discovered. At first it was called "isletin" but Macleod, in whose laboratory Banting worked, indicated that the new product would be *insulin* and shortly, through the cooperative enterprise of the Connaught Laboratories of Toronto and the Eli Lilly Company of Indianapolis, this preparation, now designated as regular or unmodified insulin, was being used widely in the treatment for diabetes.

Insulin is protein in nature and is standardized in units. A unit is the amount of the crystalline preparation required to reduce the blood sugar level of a normal fasting (twenty four hours) rabbit weighing 2 kg. from normal (120 mg. per 100 cc.) to 45 mg. per 100 cc. within five hours.

The clear aqueous solution of insulin hydrochloride known as *regular insulin* was the only insulin available from 1922 until the discovery of protamine insulin by Hagedorn of Copenhagen, Denmark, in 1936.

Regular Insulin. Regular insulin—a clear solution—when administered *subcutaneously* has a blood sugar lowering effect which is perceptible within one hour, with its greatest effect between three and six hours, after which the effect wears off—usually about seven to ten hours after the injection is given (Fig. 3). The hypoglycemic effect is greater and more prolonged when large doses are given than when the amounts injected are small.

When administered *intravenously* regular insulin exerts a perceptible reduction of the blood sugar within a few minutes with greatest effect in twenty to forty five minutes, following which the pre-injection blood sugar concentrations are usually restored between one and two hours following

acterizes the regular insulin. These two insulins lend themselves well to a method of combined therapy—one dose of protamine zinc insulin for its slow but long action and one dose of regular insulin given for action at a time when the protamine zinc insulin is least active and at a time when a prompt but short effect is desired. In the majority of cases this will be in the morning when the effect of the previous day's dose of protamine zinc insulin is on the wane, when the present day's dose of protamine zinc insulin, by virtue of its retarded effect, is not well "under way," and when quicker action than is possible from protamine zinc insulin is needed to prevent a marked hyperglycemia after breakfast and, indeed, after lunch. This combination of protamine zinc insulin and regular insulin is widely used. The practicability of mixing the two insulins is considered on page 145. Mixtures, when suitably effective, are very welcome, as they reduce the number of injections needed. However, the number of diabetics who have as good results with the mixture as with the two insulins injected separately is disappointingly small.

It may be added here that the slowness of the action of protamine zinc insulin makes it a poor agent to cope with sudden or rapidly varying demands. Hence alone it is not a satisfactory form of insulin therapy during the course of acute complications (see p. 215). Also, the number of patients in whom good control of the diabetes is possible with this insulin alone is small. Usually if the twenty-four hour insulin need is in excess of 18 or 20 units, additional rapidly acting insulin is indicated. The protamine zinc insulin is supplemented usually by one and rarely by two other doses of regular insulin or by one dose of globin insulin for most uniform results (see p. 143).

In the event of overdosage—the protamine zinc insulin being administered before breakfast—the hypoglycemic reaction is most likely to occur between three o'clock in the morning and breakfast time. This is what would be expected—at the end of the longest period in the twenty-four hours without food and with an insulin which is effective for over twenty-four hours.

Protamine zinc insulin has reduced the number of injections necessary, it has permitted measuring instead of weighing diets in all but the exceptional cases, it has made more uniform the control of the diabetes than was possible formerly, it reduces the degree of oscillation of blood sugar values and with it there is less glycosuria and fewer cases of coma and of tuberculosis in diabetic patients than occurred formerly.

Globin Insulin. Globin insulin—a clear insulin—was made available commercially in 1942 (Reiner, Searle and Lang).² It has all the general properties of insulin but with a blood sugar lowering action which is intermediate between regular insulin and that of protamine zinc insulin. Globin insulin reduces the blood sugar more slowly but for a longer time than does regular insulin and its effect is more rapid than, but not as pro-

tant cause of hypoglycemia after extra physical exercise. This feature contributes to the instability of the blood sugar concentration in children particularly.

The discovery of insulin led to increased diet allowances for the diabetic but the shortness of the blood sugar lowering effect and rapidity of action of regular insulin (Fig. 3) necessitated multiple doses in most cases when insulin was needed. Many patients needed four injections of insulin per day to control adequately the diabetes.

Crystalline insulin (zinc insulin crystals in solution) exerts effects in distinguishable, clinically from those of regular insulin.¹¹ Crystalline insulin is available on the market though its production has been greatly

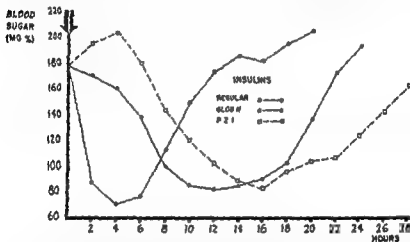


Fig. 3 The comparative effects of identical doses—60 units—of regular globin and protamine zinc insulin when administered subcutaneously to a hyperglycemic patient who received 20 gm. of carbohydrate by mouth at two hour intervals during the observations.

curtailed owing, in part, at least, to a loss of units during manufacture. It is interchangeable clinically with an equal number of units of unmodified insulin.

Protamine Zinc Insulin. This product a cloudy amorphous insulin suspension available as the result of Hagedorn's⁷ discovery (1936) and the part played by Scott and Fisher⁸ in adding zinc to protamine insulin, carried advantages which, when combined with those of regular insulin, improved greatly the lot of the diabetic patient. Protamine zinc insulin is slowly absorbed following subcutaneous injection—it is never given intravenously—and exerts a correspondingly retarded insulin effect. Also this effect is prolonged—twenty four to thirty six hours following the injection (Fig. 3). This more prolonged and more uniform effect of protamine zinc insulin, reducing the extent of the oscillations of the blood sugar concentration, is in contrast to the rapid action of short duration which char-

the total were given as protamine zinc insulin. But, a 2:1 or a 3:1 mixture, with regular insulin considerably in excess of that with which the excess protamine could combine, exerts a rapid as well as a prolonged action.

NPH insulin has a more rapid effect in reducing the blood sugar than has protamine zinc insulin and a slower effect than that of regular insulin. The initial influence on the blood sugar is almost identical with that of globin insulin which is illustrated in Figure 3.

The duration of the blood sugar lowering effect of NPH insulin is somewhat shorter than that of protamine zinc insulin. This effect is considerably longer than that of regular insulin and somewhat longer than that of globin insulin. In the event of overdosage—the insulin being administered before breakfast—hypoglycemic reactions are most likely to occur in the late afternoon, in the evening, or during the night. NPH insulin is, therefore, an insulin with an intermediate action and a product which lends itself most advantageously to mixing with regular insulin.

It would appear from three years' experience with this insulin, that a combination of NPH with regular insulin in proportion of 4:1 would permit satisfactory control of diabetes with one injection daily in a much larger number of patients than is possible with any one of the three insulins in general use. The regular insulin would serve to prevent the tendency to hyperglycemia during the forenoon and thereafter for the remainder of the twenty-four hours the action of the NPH insulin would be adequate in most cases to maintain satisfactory blood sugar values. Regular insulin tends to combine with NPH insulin if they are allowed to stand for long periods after being mixed. Hence, mixing at the time of injection is desirable.

Other Insulins. Many insulins have been tried in the search for the perfect product which would become available after injection only when it was needed. In other words, the perfect insulin should be under a control similar to that exemplified by a normal pancreas. Attempts to secure such an insulin are not to be discouraged but in the meantime we must strive for the greatest advantages that can be secured with the insulins already at hand.

Absorption of and Sensitivity to Insulin. The injection of radio active insulin and the detection of the rate of disappearance of the injected material confirmed what formerly has been assumed, i.e., the regular insulin is absorbed and disappears most rapidly. Next to disappear is the globin and the slowest to be absorbed is the protamine zinc insulin (Reimer).¹²

The rate of absorption of insulin is reduced in some cases of idiopathic insulin resistance and when insulin is injected into indurated areas. The rate of absorption in most cases determines the speed and duration of action. This is not always the case, however. In a very important group of diabetics—important chiefly because of their numerical strength—namely,

longed as, that of protamine zinc insulin (Fig 3). Globin insulin has earned a secure place in the treatment for diabetes.¹⁰ Wisely used in properly selected cases globin insulin, like each of the other insulins and combinations of insulins, has its sphere in which it is the insulin of choice. Unsatisfactory results with globin insulin indicate improper selection of the patient for this type of therapy or improper distribution of the diet or timing of the administration of the insulin. The selection of appropriate patients for their respective insulin treatments is dealt with on pages 139 to 149. Globin insulin shares, to some degree, some of the advantages of protamine zinc insulin but the specific indications for its use are when a maximum permissible dose of protamine zinc insulin fails to act quickly enough to avoid heavy reactions for glycosuria in the forenoon and yet if the dose were increased hypoglycemic reactions would occur in the early morning. In a considerable number of such cases a single daily dose of globin insulin will eliminate the necessity of a supplementary dose of regular insulin. Similarly, a dose of globin with protamine zinc insulin (not mixed) will on some occasions avoid the necessity of an injection of insulin before supper (see p 146).

Globin insulin injected subcutaneously causes a detectible reduction of the blood sugar within two hours reaching its greatest effect between six and twelve hours, with the effect subsiding from sixteen to twenty four hours (Fig 3). These effects are intensified when large doses are given—there is a more prompt effect, a greater hypoglycemic effect and one of longer duration. When used in therapy globin insulin is administered preferably one hour before breakfast and in the event of overdosage the hypoglycemic reaction is most likely to occur between 3 o'clock in the afternoon and suppertime. Patients tend to prefer the risk of a hypoglycemia during the daytime rather than in the early morning hours, as occurs in the case of an overdose of protamine zinc insulin.

NPH Insulin. A new and modified protamine zinc insulin—NPH insulin—though a relatively new preparation gives promise of earning an important place in the clinical control of diabetes. This insulin was prepared by a method developed in Hagedorn's laboratory by Krajenbuhl and Rosenberg.¹¹ NPH insulin, until recently referred to as NPH 50 insulin, is administered as a cloudy suspension of a crystalline precipitate and contains only 0.50 mg of protamine per 100 units in contrast to 1.25 mg per 100 units of the protamine zinc insulin in general use. The greatest value of this new insulin lies, in our experience, in the fact that additions of regular insulin can be made to it without sacrificing much of the rapid action of the regular insulin. In contrast, when regular insulin is added to protamine zinc insulin—containing 1.25 mg of protamine per 100 units—the regular insulin combines with the excess protamine until the ratio of the units of regular insulin to those of protamine zinc insulin exceeds 1:1. In other words, a 1:1 mixture may be expected to act the same as though

duces the serum phosphorus concentration and inhibits protein catabolism

Insulin, it is believed, exerts control over an enzyme hexokinase which in turn exerts a catalytic action on the metabolism of glucose with adenosine triphosphate to produce glucose 6-phosphate—a process which is essential before the products of insulin action mentioned above are possible. Insulin exerts an influence in at least three phases of the tricarboxylic cycle.

Insulin is rendered ineffective when given by mouth.

The middle aged obese diabetic patient is relatively insensitive to insulin. The sensitivity to insulin is increased with appropriate reduction in body weight.

Clinical observations of sensitivity to insulin are still superior to special tests.

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the overweight diabetics, usually of middle age, insulin is relatively ineffective (see p 93). This, we believe, is on the basis of an increased total metabolism. Certainly, if their weights are reduced these patients become increasingly sensitive to insulin and if their lost weight is regained so also is the relative insulin insensitivity. It is fully realized that this explanation is not complete but for practical clinical purposes it suffices until further discoveries show means for improved application in therapy.

Special tests for insulin sensitivity are surrounded by a multitude of modifying influences which may add to the confusion and, if not considered, the bland acceptance of the result as being meaningful is prone to mislead.

The lack of widespread adoption of insulin tolerance tests is evidence against their clinical value. To interpret the result properly, quantitative hormone studies on urine and serum are necessary in addition to appropriate consideration of the diet combinations preceding the test as well as complicating disorders that might alter the results, not all of which are measurable.

A modified *Radislaw test*, which shows the differences occurring between venous and capillary blood sugar concentrations four to five hours following the injection of insulin, is said to detect the source of insulin resistance, be it hepatic in origin or in the peripheral tissues.

Himsworth's test of insulin sensitivity comprises the administration of insulin by vein and glucose by mouth simultaneously and observing the effect on the capillary blood sugar at short intervals for one and one half hours. The patient is considered insulin sensitive if the expected rise of the level of the capillary blood sugar is prevented by the insulin and insulin insensitive if the capillary blood sugar values increased as though little or no insulin had been given. The lack of uniformity of results has prevented this test being of clinical value in general.

It would seem highly probable that these tests are measures of hepatic responses and that the lack of uniformity results from the fact that the influences on liver functions are legion. This is in keeping with the views of Soskin and Levine.¹²

SUMMARY

Insulin was discovered by Banting and Best in 1921. It is available in four forms: *Regular insulin* with rapid action of short duration, approximately six to eight hours; *Globin insulin*, with a slower and longer action sixteen to twenty four hours; *Protamine zinc insulin*, which goes into action slowly but exerts a blood sugar lowering effect for twenty four to thirty six hours; and the fourth insulin—*NPH insulin*—with an intermediate effect.

Insulin used clinically lowers the blood sugar, reduces glycosuria in the diabetic and increases the deposits of glycogen in the muscles and liver. It exerts an antiketogenic effect, raises the respiratory quotient, re-

duces the serum phosphorus concentration and inhibits protein catabolism

Insulin it is believed exerts control over an enzyme hexokinase which in turn exerts a catalytic action on the metabolism of glucose with adenosine triphosphate to produce glucose 6-phosphate—a process which is essential before the products of insulin action mentioned above are possible. Insulin exerts an influence in at least three phases of the tricarboxylic cycle

Insulin is rendered ineffective when given by mouth

The middle aged obese diabetic patient is relatively insensitive to insulin. The sensitivity to insulin is increased with appropriate reduction in body weight

Clinical observations of sensitivity to insulin are still superior to special tests

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CHAPTER VII

Carbohydrate Metabolism and the Blood Sugar

Introduction. Custom, arising from early investigative work, has led physicians to consider diabetes a disorder primarily of carbohydrate metabolism. Gross changes in the metabolism of carbohydrate certainly accompany the changes which characterize this disease. However, with means available to investigate pure rates of synthesis and degradation of body constituents, it is clear that there is a fundamental metabolic pool¹ in which the products of carbohydrate, protein and fat mingle and that *hypo insulinism (diabetes)* is characterized by a reduction in fatty acid synthesis, a decreased glycogen production and, in the more severe states, accelerated protein breakdown. It is clear too from the clinical standpoint that carbohydrate is but one of the important dietary factors to be considered. In fact, the total caloric intake when reduced has a more profound ultimate effect in controlling the diabetes than have reductions in the carbohydrate intake unless the total calories are reduced also.² A maximum effect in reducing the need for insulin might be expected when both carbohydrate and total calories are reduced and when physical activity is a prominent feature. This is exactly what occurs, and in treating the obese diabetic both dietary restrictions are permissible, exercise is encouraged and, in such cases, these features provide, short of insulin therapy, the most powerful means of controlling diabetes.

Carbohydrate is more prompt in its effect on the diabetic state, whether added or reduced than are changes in protein, fat or total caloric intakes. Carbohydrate is indispensable and is the most readily available food for energy purposes. It affects the level of the blood sugar immediately upon its absorption. Because of the promptness of the effect of carbohydrate on the yardstick by which we determine the control of diabetes—referring to the blood sugar level—it is appropriate to deal with carbohydrate metabolism and the blood sugar in some detail.

CARBOHYDRATE—SOURCE, DIGESTION, ABSORPTION

Source. In the normal diet the chief sources of carbohydrates are cereals (including grain products), vegetables, fruits, syrups, and sugars. Ordinarily, the sugars and syrups are not included in the diabetic's diet,

the reasons being that, with some restriction in the total carbohydrate intake it is preferable that concentrated forms be avoided, permitting liberal helpings of fruits and vegetables which carry the added advantages of providing minerals and vitamins. It is estimated that 58 per cent of protein foods, and 10 per cent of fatty foods, are available in metabolism as carbohydrate. Hence, the theoretical glucose equivalent (G.E.) of a diet is

$$\text{Carbohydrate} + 0.58 \text{ protein} + 0.10 \text{ fat}$$

Digestion. Carbohydrate foods on ingestion are subjected, while still in the oral cavity, to the action of ptyalin—secreted by the salivary glands—which on mixing with the foods, initiates the conversion of starch to maltose, and glycogen to dextrose. This process is continued in the stomach until the salivary amylase activity is stopped and acid hydrolysis substituted when the hydrochloric acid becomes mixed with the food. The digestion is continued in the alkaline medium of the small intestine by the pancreatic amylase and the intracellular enzymes—amylase, invertase and lactase—after the passage of the sugars into the cells of the intestinal mucosa. By selective actions these enzymes reduce the sugars to monosaccharides (chiefly to glucose but also to fructose and galactose) the state in which they are absorbed into the blood.

Absorption. It is of clinical importance, especially in dealing with hypoglycemic patients, that sugar is not absorbed in significant amounts from the stomach unless in the form of glucose and this in concentrations over 40 per cent. Hence functional or organic pyloric obstruction might prevent the correction of a hypoglycemic reaction by carbohydrate administered orally in dilute forms. Syrups, such as Blue Label Karo Syrup, because of their high concentrations of absorbable sugars are more likely to correct a hypoglycemia in event of delayed emptying of the stomach than are fruit juices which must reach the small intestine to be absorbed. It is noteworthy on the other hand that sugar to be absorbed by the small intestine must be reduced to isotonic concentrations.² It would appear that in the absence of delayed gastric emptying time, the weaker solutions, such as orange juice, would correct a hypoglycemia more readily than would 40 per cent sugar solutions. Maximum absorption of sugars takes place in the small intestine. Absorption of glucose occurs in the colon in hypoglycemic individuals but not, to a significant degree, in normal subjects.

Absorption from the small intestine involves (a) a phosphorylation process, a specific process rapidly accomplished through the combining of the sugar with the phosphate in the intestinal wall, and (b) simple diffusion, a slower and non-specific process.

The rate at which dietary sugars reach the blood is influenced by the speed of arrival of food in the intestine, the concentration of sugar, the

mixture of foods (complex mixtures delay absorption) and the available phosphorylating capacity. The quantitative absorption of sugar involves the state of the intestinal mucosa, the duration of exposure of sugar to the absorbing surface, endocrine influences (excessive thyroid activity accelerates the rate of absorption and vice versa, pituitary and adrenal cortical deficiency reduce absorption) and the adequacy of the vitamin intake.

Infections, deficient intake of B complex, and inanition inhibit the absorption of sugars. Insulin, apparently, has no effect on the absorption of sugar from the intestine.

Carbohydrate, once absorbed into the blood, is available, according to the priority existing at the time, for (a) *energy purposes with complete oxidation*, (b) *storage as glycogen in the liver and in the muscles*, (c) *conversion to fat* and (d) *distribution in the body fluids*—notably the blood—in concentrations which, under normal conditions, remain remarkably constant. The last mentioned is the supply line to all tissues.

Carbohydrate, in addition to its use as fuel, has a protective and detoxifying effect in the liver. It spares protein metabolism and has a far reaching effect on the regulation of the metabolism of fat. Fatty acids are partially metabolized in the liver but their complete oxidation takes place in the peripheral tissues. Ordinarily the amount of fatty acids in transport is small and no detectable amounts of acetone, diacetic acid or beta oxy butyric acids—using usual tests—are present in the blood or urine. However, if the fatty acid breakdown is accelerated as occurs in uncontrolled diabetes accompanying reduced carbohydrate stores and reduced carbohydrate metabolism, ketone bodies appear in the urine and finally, barring relief, they accumulate in the blood. This state is known as ketosis and in the extreme degree will cause coma—*diabetic coma*.

REGULATION OF THE BLOOD SUGAR LEVEL

The constancy of the level of the blood sugar between fixed, but not widely separated, extremes of normal is an ideal example of homeostasis. The stability of the blood sugar is the more remarkable in view of the multitude of factors which influence the amounts of glucose which enter the blood and the amounts that are withdrawn. The wide range of the adaptability of the homeostatic mechanism is appreciated when it is known that glucose can be administered intravenously at the rate of 0.80 gm per kilogram of body weight per hour and that the rate of administration can be materially increased after one or two hours without causing glycosuria (Wood, Gatt, 1915, and Jordan, 1927).

The concentration of glucose in the blood at any one time represents the equilibrium between the contributing and extracting mechanisms which when upset by disease, may permit hyperglycemia as in diabetes or hypoglycemia, as in adrenal cortical insufficiency or hyperinsulinism. Conditions which tend to affect the rate of glucose exchange to and from the

blood are listed in Table 7. The quantity of carbohydrate ingested, insulin and physical exercise are especially important daily considerations in the management of diabetes. These will be discussed elsewhere under their respective headings.

The concentration of the blood (venous) sugar, under normal conditions, remains relatively constant—70 to 110 mg per 100 cc in the fasting and 90 to 160 mg in the postprandial states—with the “giving and taking

TABLE 7
FACTORS INFLUENCING THE LEVEL OF THE BLOOD SUGAR

HYPOGLYCEMIC	HYPERGLYCEMIC
<i>Diet</i>	
Prolonged undernutrition	Excessive carbohydrate intake
Decreased rate of absorption of glucose e.g., pyloric obstruction	Increased rapidity of absorption of glucose e.g. gastro-enterostomy
<i>Physical Exercise</i>	
Increased exercise	Reduced exercise in diabetic subjects
<i>Liver</i>	
Hepatocellular damage (certain cases)	Hepatocellular damage (certain cases)
<i>Kidney</i>	
Renal glycosuria as in nephrosis	
<i>Hormones</i>	
Anterior pituitary deficiency	Acromegaly
Hypothyroidism	Pituitary dwarfism
Hyperinsulinism	Hypothyroidism
Adrenal insufficiency (cortical)	Phenochromocytoma some cases
Panhypopituitarism	Diabetes mellitus
<i>Medications</i>	
Insulin	Epinephrine
	Anesthesia
	17 hydroxycorticosterone (Compound F)
	11 dehydro-17 hydroxycorticosterone (Compound E—cortisone)
<i>Functional Nervous Disorders</i>	
Anorexia nervosa and other anorexia states	Toxemias
Neurocirculatory asthenia	Fright
	Trauma—intracranial
	Anger

mechanisms' at work. Minute changes in the blood sugar concentration accelerate or depress the rate of release of glucose from the liver. Soskin has shown that glucose administration by vein not only halts the outflow of sugar from the liver but is followed by marked increase in the uptake of sugar by this organ. This is followed by a period during which no sugar is taken up nor excreted by the liver and as the sugar content of the arterial blood decreases below its original value the liver resumes its out

put of sugar This thermostat like regulation of the blood sugar is profoundly upset when the supply of insulin is inadequate, as occurs in diabetes

The blood sugar level is lowest in the fasting state A mixed diet—protein, fat and carbohydrate—raises the concentration of sugar to a less degree than a meal containing a large proportion of carbohydrate If the carbohydrate is in a readily absorbable form such as dextrose, fruit juices and syrups, the blood sugar is affected more rapidly and usually to a more marked degree than by a mixed meal or even a meal high in starch Protein has a minimal and fat a negligible effect on the blood sugar concentration in the postprandial phase

Conditions which permit carbohydrate to reach the small intestine rapidly, as in cases of gastro enterostomy, and which speed the rate of absorption of glucose, as occurs in hyperthyroidism, account for an unusually rapid elevation of the blood sugar and also a degree of hyperglycemia greater than would occur in the normal individual

THE BLOOD SUGAR IN DIABETES

Abnormally high blood sugar concentrations are essential to the diagnosis of diabetes A concentration of sugar in excess of 130 mg per 100 cc in a specimen of venous blood taken after an eight to fourteen hour fast is usually due to diabetes, as are values in excess of 170 mg per 100 cc in blood samples taken after meals In *extremely mild* diabetes fasting and *postprandial* blood sugars may be normal and only by means of special tests (see p 77) can the disease be detected If diabetes is present even to this mild degree, acute febrile complications usually make it manifest by causing hyperglycemia and glycosuria

In *mild* untreated diabetes the fasting blood sugar may be normal in amount or it may exceed 130 mg per 100 cc but in these cases values higher than normal—in excess of 170 mg per 100 cc—usually prevail after meals

In *moderately severe* diabetes higher blood sugar concentrations are encountered—250 to 350 mg per 100 cc are not unusual

In *diabetic coma*, values between 300 and 800 mg per 100 cc are common Occasionally extremely high values are encountered such as in the case of E.D. (p 236), whose blood sugar amounted to 1150 mg per 100 cc

There is practically no difference in the sugar concentration in venous and arterial (capillary) blood in the fasting state After a meal, however, in the normal person the arterial blood sugar level is from 20 to 50 mg per 100 cc higher than that in venous blood This difference between venous and arterial blood sugar concentrations is an indication of the quantity of sugar withdrawn from the blood to be oxidized, converted to

fat or stored as glycogen. As might be expected, this difference is less in untreated and uncontrolled diabetes.

The magnitude of the fluctuations in the concentration of sugar in arterial blood far exceed those observed in venous blood. Also, the incidence and degree of error is usually greater when capillary blood is used for blood sugar determinations. For clinical purposes, we prefer venous blood sugar determinations, probably because it is with this method that we have had most experience. The practice of using venous blood for this purpose is almost universal in America and the method most widely used in determining blood sugar values is that of Folin and Wu, whereas capillary blood is the more widely used in Europe and the methods employed for quantitative sugar analyses are those of Bang, Hagedorn and Jensen and McLean. Blood sugar values by the Folin and Wu method include nonglucose reducing fractions—glutathione, cysteine, ergothioneine, creatinine and others as yet unidentified which have been considered to be rather constant and which account for 10 to 30 mg per 100 cc. However, Mosenthal⁴ reports that these nonglucose reducing substances exceeded the upper limit of 30 mg per 100 cc in a considerable proportion (38 per cent) of 200 consecutive cases studied and as a result advocates that the true glucose values be determined. He recommends the micro method of Lauber and Matucci⁵ for this purpose.

In the usual management of diabetes and even in most diagnostic studies, experience has shown the macro method of determining the blood sugar (true blood sugar plus other reducing substances) to be satisfactory. However, in borderline cases, unusually high concentrations of nonglucose substances might tip the scales toward an unjustified diagnosis of diabetes. In such cases, true glucose values would be of special importance. The other alternative and the one we have used is to do a series of tests using the macro method of determining the venous blood sugar values before making a definite decision.

The major sources of glycogen are preformed carbohydrates—sugars and starches—and proteins of the diet. Glycogen is formed during fasting states from noncarbohydrate sources by the liver. This process is gluconeogenesis. This is an important source of sugar during fasting in the normal and one that is drawn upon heavily in uncontrolled diabetes. Also, gluconeogenesis is affected by adrenal cortical hormones, removal of which reduces tissue protein breakdown. Conversely, the injection of an excess of these hormones increases the rate of protein breakdown, making available glucose from the metabolism of the resulting amino acids.

Carbohydrate is the chief source of energy in the body. Energy is liberated throughout the dissimilation of carbohydrate by means of certain phosphorylation processes, the completion of which depends upon enzymatic activity, a long period of which takes place in the conversion of gly-

and for each molecule of O_2 absorbed a molecule of CO_2 is formed. Hence, if carbohydrate only is being metabolized, the RQ is 1.0. During the metabolism of fat alone the quotient is 0.71, for protein it is 0.80, for alcohol it is 0.67 and on an ordinary mixed diet the RQ is about 0.85. The quotient is taken as an indication of the type of food being metabolized—the closer to 1.0 the higher is the percentage of carbohydrate and the closer to 0.7 the higher is the percentage of fat being utilized. Although these assertions are generally correct, physiologists caution that if fat is being transformed to carbohydrate a low RQ is to be expected but the conditioning influences of the conversion process and the ultimate metabolism of the carbohydrate are not to be lost sight of.

In uncontrolled diabetes the RQ tends to be low in keeping with the reduced amount of carbohydrate metabolized and with the acceleration of fat catabolism. Insulin therapy reverses this trend and markedly so if an ample carbohydrate intake is maintained.

The respiratory quotient can be determined for experimental purpose by measuring the amount of oxygen consumed and the amount of carbon dioxide produced per hour.* Correction for the amount of protein metabolized is necessary before the nonprotein RQ can be calculated. Each gram of nitrogen excreted in the urine assuming that the renal function is normal indicates that 6.25 gm. of protein have been oxidized. Knowing the total nitrogen excretion it is possible to calculate the oxygen and carbon dioxide that have to do with the metabolism of the protein and to deduct these amounts from the total respiratory exchange. From this information and with a known RQ it is a simple matter to calculate the amounts of protein, fat and carbohydrate oxidized over a given period. The reader is referred to standard texts on physiology for further details.

* According to Avogadro's law equal volumes of gases with the same pressure and temperature contain an equal number of molecules. To metabolize 100 gm. of glucose 75 litres of oxygen are required from outside and for the oxidation of the carbon

and 75 litres of carbon dioxide are produced. The RQ is therefore $\frac{CO_2}{O_2} = \frac{75}{75} = 1$.

In the combustion of fat rich in carbon and hydrogen and relatively poor in oxygen 200 litres of O_2 are needed and 142 litres of CO_2 are produced. The RQ is

$\frac{142}{200} \approx 0.71$ (Dewar and Taylor)

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CHAPTER VIII

Disturbed Physiology in Diabetes

Introduction. In diabetes the storage of glycogen in the liver and in the muscles is impoverished and the utilization of sugar by the tissues is reduced. There are no detectable differences between the physiologic processes of the normal and those of the diabetic patient whose diabetes is under perfect control. This fact presents the most logical reason for adequate control of the diabetes when it is possible to do so. The disturbed physiology characteristic of diabetes occurs when the diabetes is "out of hand" and the degree of severity of the uncontrolled diabetes influences greatly the magnitude of these disturbances. It is with this concept in mind that the abnormal processes are dealt with.

The storage of monosaccharides, notably glucose, as glycogen, following their absorption from the small intestine and transit by way of the portal system to the liver, is greatly reduced in diabetes. As a result large quantities of sugar gain access to the systemic circulation and this excess is made greater because of a reduced ability of the diabetic properly to utilize sugar. The concentration of the blood sugar is increased to hyperglycemic levels and when these exceed the renal threshold—0.160 to 0.180 mg. per 100 cc. in venous blood—for variable periods glycosuria results. Sugar is lost in the urine in amounts varying from minute traces to several pounds per day. A unique type of starvation ensues—the extent of which is directly related to the amount of glycosuria.

In moderately severe and severe diabetes sugar is lost in the urine even during fasting. The sugar is derived from the diminishing supply of hepatic glycogen at first and later an emergency source, the body protein, is tapped in nature's attempt to provide sugar for vital functions. An index of the excessive protein breakdown is to be found in the increased excretion of nitrogen in the urine—each gram of urinary nitrogen indicates the metabolism of 6.25 gm. of protein and the normal excretion of nitrogen in twenty-four hours varies from 10 to 14 grams. Quantitative determinations of the nitrogen excretion are not necessary in the clinical management of diabetes. It suffices to know that in uncontrolled diabetes, of more than a mild degree of severity, body protein is being sacrificed, muscles become wasted and the patient's lassitude is intensified. This loss of body protein

has played a large part in making poor risks of diabetic patients for surgical procedures in the past and in causing lowered resistance to infections, and in the development of other hormonal deficiencies occurring as a direct result of malnutrition

As the loss of sugar increases the metabolism of fat is also accelerated. This is not detectable clinically in the early phase, as the peripheral tissues can metabolize a small increase of the ketone bodies which are transported to them after their production in the liver. However, as the production of ketone bodies exceeds the amounts utilized in the peripheral tissues acetone bodies appear in the urine and finally in the blood in amounts detectable by crudely quantitative tests (see p. 67). A digest of the clinical outcome of the disturbed physiology as it occurs in diabetes is presented in Table 8.

TABLE 8

THE CLINICAL OUTCOME OF THE DISTURBED PHYSIOLOGY IN DIABETES

Hypo insulinism (Diabetes)	→	Retarded ability to store and utilize glycogen Overproduction of glucose by liver	→	Hyperglycemia and Glycosuria	→	Polyuria
						Increased nitrogen excretion
						Acetonuria
						Hyperketonemia (ketosis)
						Dehydration
						Deminerallization
						Loss of weight
						Asthenia
						Decreased resistance to infection
						Degenerative disorders

The means are available to correct these deficiencies. In the early phases a normal status is promptly restored by insulin therapy and a suitable diet. In the latter phase that of advanced ketosis, a reversion of the abnormal processes is still possible but at this stage the treatment is more complicated because of the dehydration and the disturbances in electrolyte balances which have intervened (see Chapter XVII).

The salient features of the chain of events which characterize diabetes mellitus as seen clinically are summarized as follows: (a) *hyperglycemia* and *glycosuria*. Among sequelae of these abnormalities are acetonuria, increased ketonemia (ketosis), polyuria, dehydration, demineralization, loss of weight, asthenia and decreased resistance to infection. (b) *Degenerative disorders*. Diabetic retinitis and cataract, disease of the coronary arteries, renal and peripheral vascular disease and the neuropathies are chronic complications of disturbed physiology over long periods. The success in controlling hyperglycemia and glycosuria will be rewarded by the prevention or attenuation of these complications.

Hyperglycemia The relative influences of a disturbed regulation of carbohydrate metabolism with *overproduction of glucose by the liver*, and with the failure to store glycogen to a normal degree, and *impaired utilization of glucose by the tissues* as causes of hyperglycemia are not entirely understood. Soskin¹ champions the convincing overproduction theory in keeping with which insulin prevents overproduction of sugar by the liver.

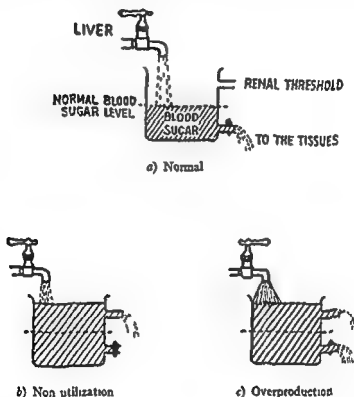


Fig 4 Diagrammatic analogy illustrating the non utilization and overproduction theories of diabetes (after Soskin)¹

an inhibiting effect which is reduced in the insulin deficient state—diabetes. **Hyperglycemia** ensues.

The replacement of glycogen in skeletal muscles following physical exercise is retarded in uncontrolled diabetes² and as the skeletal muscles provide the overwhelming bulk of metabolically active tissues of the body this is of great significance. All are agreed that insulin facilitates the transit of glucose into the tissues and facilitates its activity in cellular metabolism and that these activities occur as a direct result of increased phosphorylation made possible by insulin activity. In uncontrolled diabetes these functions are profoundly disturbed and as a result the sugar is not withdrawn

from the blood as rapidly as under normal circumstances and with the liver releasing sugar at an increased rate *hyperglycemia* results

Nondiabetic hyperglycemia may occur following intracranial injuries (infection or trauma, in shock and following the administration of anesthetics) Hyperglycemia under these conditions is transitory, not lasting more than a few hours, and the mechanisms of its production are disturbed nervous control of releasing sugar from hepatic glycogen and stimulation of the adrenal medulla

Glycosuria Glycosuria, as detectable by the usual tests—Benedict's, Clinistest and Galatest—does not occur under normal conditions In the untreated diabetic glycosuria is the rule It is most frequent after meals and is least and may be absent before breakfast It usually occurs when the concentration of the sugar in the venous blood exceeds values of 160 to 180 mg per 100 cc Under unusual circumstances this so-called *renal*

TABLE 9

GLUCOSE CONTENT OF BODY FLUIDS NORMAL AND IN UNTREATED DIABETES

FLUID	NORMAL	DIABETIC
	Glucose (mg per 100 cc)	
Whole blood	60-90	110-750
Plasma	70-110	130-800
Serum	70-110	130-800
Lymph	70-110	130-800
Cerebrospinal fluid	40-70	75-400

threshold may be lower than 160 mg per 100 cc—a low renal threshold—and the glycosuria resulting in the nondiabetic under these circumstances is known as *renal glycosuria* or *diabetes innocens*—a poor term A low renal threshold occasionally is present as a complication of diabetes The relationships of blood sugar production, rate of utilization and hyperglycemia to the renal threshold are depicted schematically in Figure 4

Glycosuria is considered as being due to diabetes until proved otherwise, because it is due to diabetes much more frequently than to any other disorder and because, if the diagnosis of diabetes is missed, irreparable harm may be done The differential diagnosis of sugar in the urine is dealt with on page 37

The sugar contents of the various body fluids in normal and in diabetic subjects are indicated in Table 9

Ketosis Ketone bodies (acetoacetic acid, beta hydroxybutyric acid and acetone) are normally produced almost exclusively in the liver and transported in the blood for utilization by the tissues The quantities of ketones produced from fat far exceed those from other sources In fact the degree of ketosis is an index of the catabolism of fat and there being no reduc

tion in the ability of the peripheral tissues to dispose of ketone bodies in the diabetic an excess of ketone bodies in the blood must mean that they are being produced in abnormally large amounts

Normal carbohydrate metabolism with an adequate intake of carbohydrate and total calories and normal stores of glycogen are the factors which prevent excessive breakdown of fat. On the other hand, during starvation or in the case of uncontrolled diabetes, when large quantities of sugar are lost in the urine, less sugar is metabolized and glycogen storage is depleted. As a result an increase in fat metabolism occurs.

A liver with a good store of glycogen turns out sugar but when this store is depleted, and the fat content of the cells of the liver increases, the metabolic process becomes one of increased ketone production.* When the accelerated production of ketone bodies exceeds the amount removed from circulation by the peripheral tissues the excess, at first, is excreted in the urine (*ketonuria*). Eventually, when the excretory mechanism is unable to keep pace with the production the ketones accumulate in the blood (*hyperketonemia*), as occurs in diabetic coma. Insulin is the most potent antiketogenic agent known. It produces this effect by preventing the deposition of fat in the liver, by restoring glycogen storage in this organ and especially by facilitating the metabolism of carbohydrate, an effect which promptly reduces the excessive production of ketones.

Alloxan Diabetes Islet cells of the rabbit's pancreas are selectively destroyed and diabetes is caused by a single intravenous injection of alloxan,^{3, 4} 150 to 200 mg per kg of body weight. Diabetes is produced in dogs when 50 to 75 mg of alloxan per kg are given. Larger doses cause uremia plus diabetes. An initial hyperglycemia lasting fifteen minutes to one hour follows the injection of the alloxan. This, in turn, is followed by a marked hypoglycemia with convulsions. The hypoglycemia is due presumably to insulin released from damaged islet cells. Finally hyperglycemia and permanent diabetes ensue.

The damage to the islets is completed with great rapidity—alloxan is not detectable in the blood for longer than five minutes after its injection intravenously.

Alloxan diabetes is of great interest to investigators because Alloxan is chemically related to uric acid—a normal constituent of the body, the glutathione concentration normally present in the blood is greatly reduced after the administration of alloxan, glutathione administered in large doses protects against the islet cell destruction by alloxan, transient diabetes has been reported to follow the intraperitoneal injections of uric acid in rabbits,⁵ but this only occurred when the blood glutathione levels were reduced by means of diets deficient in cystine and methionine and also

* Aceto-acetic (diacetic) acid is formed first. It may be reduced to beta hydroxy butyric acid and this process may be reversed. Acetone is an oxidation product of one or other of its precursors—diacetic acid or beta hydroxybutyric acid.

on the basis that injections of purified adrenocorticotrophic hormone (ACTH) produced in man a transient diabetes associated with a consistent correlation between loss of tolerance for carbohydrate, increased endogenous parane metabolism and depressed levels of blood glutathione⁴

The clinical significance of alloxan diabetes is that it permits the exploration of this problem from a new approach

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CHAPTER IX

Pathology of Diabetes

INTRODUCTION

Few diseases cause more widespread pathologic changes than does diabetes. Most of the changes characteristically seen are those associated with premature aging: the degenerative diseases of the arteries are outstanding. Because of the inconstancy of cellular abnormalities, the occurrence of normal tissues in patients with severe diabetes and the occurrence of the

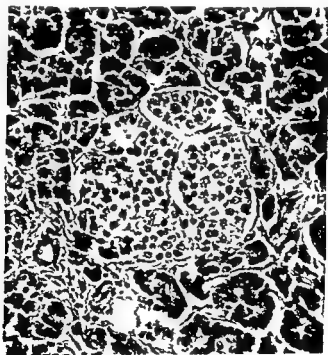


Fig. 5. Normal islet of Langerhans.

occasional identical changes in the pancreas of the diabetic and of the non-diabetic diabetes can be diagnosed on morphologic grounds alone in but a small percentage of cases.

The most consistent pathologic changes in diabetes are those of accel

erated degenerative processes These are especially discernible in the circulatory system, the eyes, kidneys and nervous system Changes in the pancreas are disappointingly inconsistent

PANCREAS

A. Acute Changes *Acute degenerative changes, notably hydropic degeneration of the islets of the pancreas, can be produced in experimental diabetes* A normal islet is illustrated in Figure 5, and acute hydropic degeneration of the islets—a reversible state—is depicted in

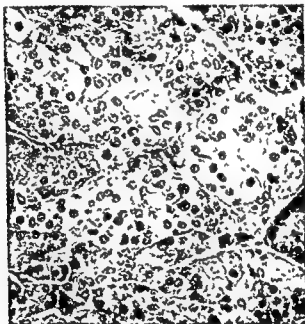


Fig 6 An advanced stage of hydropic degeneration of the cells of the islets of Langerhans (Courtesy of Dr F M Allen.)

Figure 6 Partial pancreatectomy—nine-tenths of the pancreas being removed—followed by overfeeding causes hydropic degeneration and, barring relief by appropriate treatment, exhaustion and death of the islet cells Also, in producing diabetes by injecting an extract of the anterior pituitary gland this form of degenerative change is noted¹ (p 5), and when hyperglycemia is maintained by the intraperitoneal injection of glucose, hydropic degeneration of the islets occurs (p 15) Hydropic degeneration does not occur in alloxan diabetes, in which case there is chemical destruction of the insulin producing cells—the beta cells—in contrast to the overworking exhaustion, and functional death of these cells brought about by overfeeding the partially depancreatized animal and by the ad

ministration of an extract of the anterior pituitary gland. On the basis of these changes, observed at will in experimental diabetes, it is highly probable that hydropic degeneration of the islets occurs in nearly all, if not all diabetic patients at one time or another. The fact that hydropic degeneration first noted by Weischelbaum (1901), is detected only occasionally on examination of tissue secured at autopsy, or by biopsy, in the human is no evidence that this degenerative change is not an essential feature in the development of clinical diabetes. If one could select the time that would be most propitious for observing hydropic degeneration it would

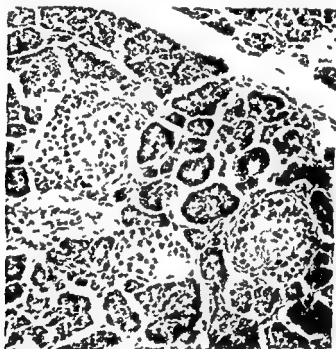


Fig. 7 Bands of interacinar fibrosis and three islets which have undergone extensive hyaline degeneration' (Courtesy of Dr. F. M. Allen)

be in that period shortly after the onset of the clinical manifestations of diabetes and when the intensity of these manifestations were not modified by treatment, or during the progression of a fulminating diabetes. The impracticability of this procedure doubtless deprives us of the positive proof that hydropic degeneration is an indispensable phase in the pancreatic change in diabetic patients. Hydropic degeneration is an acute and transitory process.

The destructive process of hydropic degeneration is, in some cases, accompanied by attempts at regeneration by the islet cells. Mitotic figures may be seen, particularly at the periphery of the islet clusters. That these

new cells may be more readily destroyed than the more mature cells by the functional overstrain that exists is possible and this phenomenon could explain why they do not save the situation. Furthermore, the stimulus to new cell production may subside with control of the diabetes. One might speculate that if it were possible to stimulate islet cell hyperplasia or regeneration and yet keep the diabetes under control adequate cells might reach maturity in sufficient numbers to cure the diabetes. There is much experimental evidence that, if there is adequate treatment before irreparable degenerative changes have taken place hydropically degenerated cells can be redeemed and all manifestations of diabetes can be overcome.

Lymphocytic infiltration of the islets occurs in children with severe diabetes and is considered as an acute process. *Acute inflammatory changes* in the pancreas are not characteristic of diabetes and yet diabetes, on uncommon occasions follows repeated attacks of pancreatitis when most of the organ is destroyed.

B Chronic Changes Chronic manifestations of diabetes are detected with greater frequency than are the acute and transient changes. Among the chronic changes there is a *reduced number of islets of Langerhans*—although this is not invariably so—and in keeping with this, significantly less insulin is recovered from the pancreas of the diabetic—0.4 units per gram—than from that of the nondiabetic—1.7 units per gram.

Replacement of the islet cells by a hyaline substance is the most common finding in autopsy material of diabetic patients (Fig. 7). That this type of degeneration is not limited to the pancreas is well known. The arteries and kidneys are particularly involved by the laying down of hyaline material. Hyalinization of the islets is more common in patients over forty years of age but it is related more to the duration of the diabetes than it is to the age of the patient or to the degree of severity of the diabetes. The source of the hyaline and the reason for its selective localization in the islets are unknown. Hyalinization is a slow process but eventually it destroys the function of the islets which it invades and with progressive involvement of more and more islets the functional capacity of the insulin-producing mechanism is reduced proportionately. It is not known whether hyalinization is a cause of, or the result of diabetes.

Fibrosis is next in frequency to hyalinization as a chronic change in the pancreas of the diabetic patient. Also it is primarily a lesion of the islets and there is little extension into the acinar tissue. It is present in slightly over half of these patients. The cause of the fibrosis is not known. Extension is along the course of the vessels of the islets and it is most common in patients over forty years of age.

C Pancreatic Lesions with Secondary Diabetes *Pancreatic calculi* are uncommon. They may be multiple and scattered throughout the pancreas or solitary with the calculus obstructing the duct of Wirsung.

and, by setting up a retrograde autolysis, destroy the pancreas. The acinar portion succumbs first and the islets later. This is, surely, a rare cause of diabetes.

Infiltration of the pancreas by *neoplastic growths* and by changes with deposits of iron as seen in *hemochromatosis* are uncommon causes of diabetes.

EXTRA PANCREATIC CHANGES

Liver. Fatty livers develop in diabetic animals maintained on a diet deficient in choline and without insulin.² Fatty deposits also occur in the liver of untreated diabetic patients and more especially in the diabetic child. These deposits disappear quickly and the size of the liver rapidly lessens when the diabetes is controlled adequately, especially when choline or one of its precursors is administered freely. In the patient with uncontrolled diabetes and impending coma, *hepatic glycogen disappears from the cytoplasm of the liver cells but the nuclei of these cells become engorged with glycogen.* These changes are reversible.

Skin. The skin is an organ of considerable importance as a storehouse for glycogen but in uncontrolled diabetes the glycogen stores in the skin become depleted while the sugar content of the skin may be nearly treble that of the nondiabetic because of the systemic hyperglycemia. Other cutaneous evidences that may be associated with diabetes and characterized by deposits of lipids—chiefly cholesterol—in the skin are *xanthelasma palpebrarum*, *xanthomas* and *necrobiosis lipidica diabetorum*.

Furuncles, carbuncles and pruritic disturbances are common complications of diabetes. Infections of the skin were the most common complication in 514 consecutive diabetic patients admitted to the wards of the Pennsylvania Hospital (see p. 212) because of acute complications. Xanthochromia, a yellow discoloration of the skin of the palms of the hands, soles of the feet and nasolabial folds, is due to a pigment derived from foods rich in carotene, notably the yellow foods—e.g., egg yolk, butter, carrots and sweet potatoes. Diabetic patients who ingest more yellow foods than is normally the case are also more likely to exhibit xanthochromic deposits in the skin.

1. . .

of waxy exudates, deposits of lipids, *retinitis* and *retinopathy* with hemorrhages and atheromatous changes in the larger and hyaline thickening of the media of the smaller arteries. The source of the waxy exudates is not known but there are evidences that they are hyalinized deep retinal hemorrhages which result from venous stasis and rupture of veins. Capillary aneurysms in the inner nuclear layer of the retina give the appearance of petechial hemorrhages.³ Superficial flame-shaped hemorrhages are arterial in origin and occur more frequently in the hypertensive diabetic but hyper

tension is by no means necessary for this type of lesion to occur. Increased capillary fragility is a common finding in these cases. There is no apparent direct relationship between hypertension and the deep retinal hemorrhages of venous origin.

A proliferative retinitis may take the form of a dense white fibrous membrane developing in hemorrhagic areas or the formation of new vessels to be seen most frequently about the optic disk. Both of these abnormalities are distressingly common.

The foregoing changes in the eyes are directly related to the duration of the diabetes and to the poor control which has been exercised over this

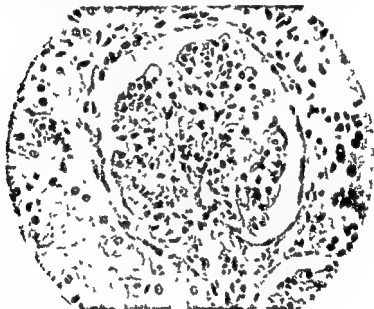


Fig. 8 A normal renal glomerulus

disorder for long periods. Cataracts, indistinguishable from senile cataracts, are somewhat more common, but not strikingly so, in the older diabetics than in the nondiabetic population. True diabetic cataracts are seen in young patients. Fortunately they are rare.

Kidneys *Intercapillary glomerular nephrosclerosis*, as described by Kimmelstiel and Wilson,⁴ is of major importance because of its frequency and because the incidence of this complication is increasing. In its advanced stage this disorder is indicative of diabetes. There is a hyaline material laid down between the capillary loops progressing until all segments of the glomerular tuft are involved and forming rounded hyaline masses in the glomeruli. Multiple segments of the tufts may be involved

with eventual replacement of the entire glomerulus (Fig 9) A normal glomerulus is illustrated in Figure 8 An advanced degree of arteriosclerosis with its subintimal deposits of hyaline substance is usual in these cases (Figs 10 and 11) The clinical counterpart is indicated by edema arterial hypertension and albuminuria The reduction of renal function ultimately causes uremia This disease process occurs in a mild form in both diabetic and nondiabetic subjects It may remain relatively stationary for long periods but when the edema and albuminuria are of great degree and the serum albumin is reduced the duration of life is measured in months and not in years



Fig 9 Intercapillary glomerulosclerosis in diabetes mellitus Note characteristic nodular hyaline thickening in one segment of the tuft and the diffuse intercapillary sclerosis

Arteriosclerosis involving the renal arterioles is the most common renal disorder associated with diabetes In diabetic patients over fifty years old it is found in 77.6 per cent or about five times as frequently as in non-diabetic controls⁵ The characteristic changes, i.e. subintimal deposits of hyaline are much more intense in diabetic subjects In fact thick homogeneous deposits of hyaline substance in afferent and efferent renal arterioles present strong presumptive evidence of diabetes This change illustrated in Figures 10 and 11 is contrasted with normal renal arterioles as depicted in Figure 12

The degree of arteriosclerosis appears to have a direct relation to the degree of arterial hypertension in patients under fifty years of age though arteriosclerosis occurs even in severe degrees (Fig 11) in diabetic pa-

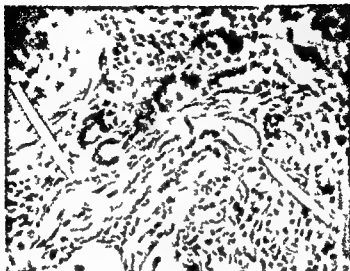


Fig 10 Arteriosclerosis of an afferent arteriole leading into a glomerulus (lower right) in a kidney of a diabetic patient

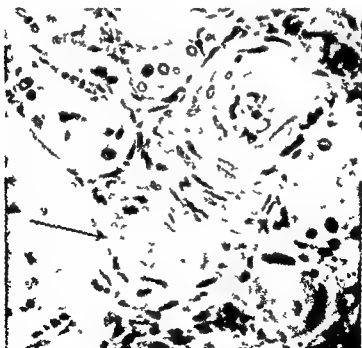


Fig 11 Severe renal arteriole sclerosis in a diabetic patient

tients without hypertension. In individuals over fifty years of age the degree of involvement is related more to advancing age than it is to the degree of hypertension.

There is good evidence that diabetes in some manner, intensifies the speed and degree with which the hyaline deposits in the arterioles are made.

Malignant hypertension a rapidly progressive form of hypertension with uremia secondary to thrombotic glomerulitis or intimal fibro-

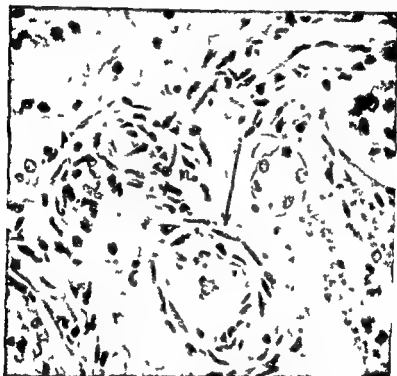


Fig. 12 Normal renal arteriole.

sis, may be encountered in association with diabetes but there is no specific relationship between the two diseases.

Pyelonephritis is a common complication of diabetes. Of 60 of our diabetic patients coming to autopsy between 1927 and 1942 21 had evidences of active or healed pyelonephritis. The disease may take an acutely destructive form—necrotizing renal papillitis—with extensive abscess formation and necrosis of the papillae.⁶

Arteriosclerotic changes in renal arteries occur in diabetics with greater frequency than in nondiabetic subjects but morphologically the disorder is the same in both.

Arteries Lesions of the vascular system are responsible for the deaths

in more than 50 per cent of patients who have diabetes for more than fifteen years. Sclerotic changes in the coronary arteries predominate as do similar changes in the arteries of the pelvis, legs and feet (Fig 13). Irreversible changes are represented by swelling and hyaline degeneration of the ground substance of the intima and the infiltration of lipids and subsequent calcification. These processes—atheromatous and arterioscle-

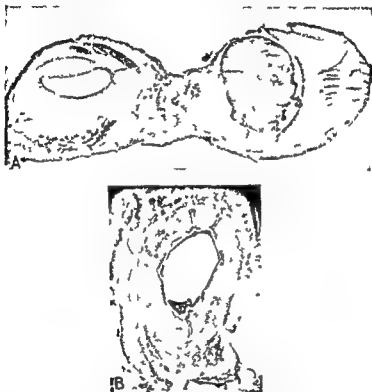


Fig 13 A A section of two medium sized arteries near their junction. Each shows a marked encroachment of the lumen by a hyaline thickening of the intima and one shows in addition the occlusion of the lumen by a thrombus.

B A section of a normal artery of approximately the same size is shown for comparison.

rotic—are seen most frequently in the aorta, the coronary arteries and the vessels of the extremities. Hence the predisposition to occlusion of the coronary arteries and to occlusive vascular disease of the extremities is not surprising.

A third type of vascular degeneration involves the medium sized vessels causing irregular medial necrosis and calcification without lipid deposition. This is Monckeberg's sclerosis.

Nervous System Not much is known of the pathologic changes in the neurologic complications of diabetes. Demyelination of the nerves occurs in cases of *diabetic neuritis* which is the predominating acute and reversible neurologic complication of diabetes. The degenerative changes of the *diabetic neuropathies*—the characteristically chronic neurologic complications—occur in the peripheral nerves anywhere in the entire nervous system, and in the spinal cord particularly in the posterior and lateral columns and are identical with those seen in pernicious anemia. These changes account for the disturbances in sensation the so-called diabetic *tibias* and in rare cases, changes in the bones and joints of the feet indistinguishable from Charcot's joints and trophic ulcers of the feet (see p 207). These neurologic changes have been attributed to arteriosclerosis. This is not the whole answer however as they occur in some instances in the absence of significant arteriosclerosis. Infection is the apparent cause in some but not all cases. The degenerative changes of advanced degree in which the process may be irreversible are distinct from those in which acute inflammatory changes predominate. The acute changes as seen in neuritis are readily cured primarily by control of the diabetes and less frequently by correction of dietary deficiencies notably a deficiency of vitamin B₁.

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CHAPTER X

The Urine and Blood in Diabetes

THE URINE

Glycosuria In general, the term "glycosuria" is loosely used to mean sugar in the urine in the broad sense and is not restricted to glucose in the urine as occurs in diabetes. A relatively innocent glycosuria occurs in some nondiabetic subjects who have permanently low renal thresholds for glucose, and others whose renal thresholds are temporarily reduced as occurs during pregnancy and in hyperthyroidism. Other sugars, as discussed on page 90, may be excreted in the urine but this is an uncommon occurrence and is of little or no clinical significance.

Glucose, a fermentable, dextrorotatory, copper reducing sugar appearing in the urine in amounts demonstrable by the Benedict and other tests* in common use, should be considered as being due to diabetes until proved otherwise. It is a simpler matter to establish the diagnosis of diabetes and thereby identify the sugar as glucose indirectly than it is to identify the sugar by chemical means. A search for hyperglycemia after the strain of a meal usually will give the answer if the patient has diabetes but if doubt still exists the special tests presented in Chapter XI are resorted to. Glycosuria is the most common, though not the most sensitive indication which leads ultimately to the diagnosis of diabetes mellitus. Ordinarily glycosuria is the result of hyperglycemia, sugar being lost when the venous blood sugar level exceeds the renal threshold, usually between 160 and 180 mg per 100 cc. Glycosuria is of special importance because it is tested for in the conduct of a routine urinalysis, hence the chance of its discovery is great and the detection of the diabetes is more likely in contrast with the more delicate, but less frequently performed, test for diabetes. ~~via, determination of the level of the blood sugar~~

There is a copper reducing substance in normal urine but the quantity is so minute that it escapes detection by the usual tests. Sugar occurring in the urine in concentrations below 0.1 per cent may be considered as normal. Glucose when boiled with an alkaline copper solution (Benedict's test, p. 67) reduces the copper to cuprous oxide, thus changing the color of the solution from blue to green, greenish yellow, orange or brick red.

* Clinitest and Galatest, see p. 67.

with increasing concentrations of sugar. Ordinarily, glucose occurring in sufficient quantities in the urine to be detected by the Benedict test indicates a pathologic condition. Glycosuria may occur in some normal persons for short periods after an unusually great carbohydrate intake. This is *alimentary glycosuria* and may be attributed to a lowered renal threshold or to absorption of glucose from the intestine at a rate too rapid for its prompt removal from the circulation. Starving individuals may have glycosuria upon the resumption of feeding (*hunger glycosuria*). These are innocent forms of glycosuria.

The glycosuria which occurs as the result of diabetes varies from scarcely detectable traces to large amounts, 10 per cent or more. It is unusual, however, to find a concentration of sugar in the urine of diabetic patients in excess of 10 per cent. For practical purposes qualitative tests (p. 67), which are crudely quantitative also, applied to fractional collections of urine serve admirably as guides in adjusting the insulin dosage. More will be said of this in the section on treatment.

In the case of a patient having a mild diabetes, glycosuria is most likely to occur during the daytime and in the evening, that is, during the time of day when three meals are taken in fairly close succession. Under these circumstances glycosuria is least likely to occur in the morning before breakfast—at the end of the longest period without food—and an evening specimen, not the first one voided in the morning, is the one most likely to contain sugar. In contrast, the severe grades of diabetes cause continuous glycosuria until corrected by appropriate treatment.

When sugar is found in the urine, and the blood sugar values are normal, both before (fasting) and two hours after a liberal meal, and when the patient is subjected to a glucose tolerance test, the diagnosis of a non-diabetic melituria is justified.

False positive reactions to tests for glycosuria are common. The copper used in qualitative tests for glycosuria is slightly reduced and may be mistaken for sugar when large quantities of conjugated glycuronates occur in the urine. They appear in decomposing urine and may be avoided by examining freshly voided specimens. The glycuronates appear in the urine in considerable quantities and give a mildly positive Benedict's test after the ingestion of salicylates, menthol, chloral hydrate, morphine and amino pyrine. As a group, the glycuronates reduce the copper in Benedict's and Fehling's solutions but, unlike glucose, are nonfermentable.

The homogentisic acid of alkaptonuria reduces the alkaline copper solutions, thus giving false positive tests for sugar. In this disorder, if the urine is allowed to stand and become alkaline by ammoniacal putrefaction or if alkali is added, it assumes a black or gray color. Alkaptonuria is a rare condition.

Tests for Glycosuria. For mass examinations, for office and clinic prac-

tice, the following simplified tests for sugar and acetone in the urine are satisfactory. Also they are employed as routine by diabetic patients who test their own specimens.

CLINITEST FOR GLYCOSURIA * This convenient modification of Trommer's test permits a qualitative, and crudely quantitative, test, for sugar in the urine. The test is made by placing 5 drops of urine in a test tube, the dropper is rinsed and 10 drops of water are added, then one Clinitest reagent tablet—containing anhydrous copper sulfate, anhydrous sodium hydroxide, citric acid and sodium bicarbonate—is added. Heat is generated by the chemical reaction in the tube causing the solution to boil. The test tube is not to be shaken while the solution is boiling. The result is read after the boiling has ceased for at least fifteen seconds. There is no sugar in the sample tested if the resulting color is blue. Sugar is present if the final color is dark green, yellow, orange, brown or rust red. The amount of sugar present, up to 2 per cent, can be determined with a fair degree of accuracy by contrasting the color obtained with the standard color scale.

GALATEST FOR GLYCOSURIA † This test for sugar in the urine is accurate, simple, requires no boiling and gives a prompt reaction. It is performed by placing on a piece of plain white paper an amount of the Galatest reagent—containing a bismuth salt, sodium hydroxide and sodium silicate—sufficient to cover one third of a dime. To this is added one small drop of urine. The result is read after thirty seconds have elapsed. If the powder takes on the amber color of urine the specimen tested contains no sugar. The color changes from a light gray to black with increasing concentrations of sugar. The approximate amount of sugar present is estimated by comparing the color obtained with the standardized color scale.

BENEDICT'S QUALITATIVE TEST FOR SUGAR IN THE URINE (MODIFIED)

Equipment

1 Qualitative Benedict's Solution (when purchasing testing solution, specify *Qualitative* Benedict's Solution as Benedict's Quantitative Solution does not change color when boiled with glucose)

2 Test tubes marked at 5 cc. and 25 cc. levels

3 Dropper pipette

4 Water bath

Technic

1 Put 25 cc. (approximately ½ tea-spoonful) of Benedict's Solution in a test tube.

2 Add 4 drops of the urine to be tested. Hold pipette perpendicularly while adding drops.

* Materials for this test may be secured from Ames Company, Inc., Elkhart, Ind.

† Galatest equipment is obtainable from the Denver Chemical Mfg. Co., Inc., 163 Varick St., New York 13, N. Y.

- 3 *Shake tube to mix urine and Benedict's Solution thoroughly*
- 4 *Put the tube in a water bath of boiling water and boil for five minutes*
- 5 *Let cool and read reaction*

Interpretation

Clear blue solution No sugar

Light greenish yellow Faint trace of sugar

Yellow to orange Moderate amount of sugar, about 1 per cent

Chocolate brown to brick red Large quantities of sugar, over 1 per cent

This test has the advantage of being inexpensive

Millard Smith's Micro Modification of Benedict's Quantitative Test for Sugar in the Urine

In clinical practice the exact quantitative determinations of sugar in the urine are not often necessary but this simplified method of obtaining this information if desired is included for the sake of completeness

Equipment

1 One small ring stand with test tube clamp a micro Bunsen burner or small alcohol lamp

2 A Pyrex test tube (18 by 160 mm)

3 A Millard Smith pipette No 2 and a 1 cc O-twald pipette

Technic

1 Transfer 1 cc of Benedict's quantitative solution to the test tube (held in ring clamp) and add 0.2 to 0.7 gm of anhydrous sodium carbonate Bumping is prevented by adding a thoroughly dried pebble a piece of quartz or a pinch of talcum powder

2 The mixture is raised to and kept at the boiling point

3 The urine is added slowly from the Smith pipette until all of the blue color disappears Care should be taken to allow time for complete reduction before adding more urine The test is done slowly and care must be taken not to pass the end point The percentage of sugar present is read directly from the pipette without calculation Urine containing less than 1 per cent of sugar is titrated directly When larger amounts of sugar are present the urine is diluted 1:10 or 1:20 before titration

Specific Gravity. The specific gravity of the urine usually increases in direct proportion to the amount of sugar present A specific gravity of 1.030 or above, obtained on a pale urine is almost without fail, due to sugar The specific gravity is restored to normal when the glycosuria is corrected However, a normal specific gravity, 1.010 to 1.025, is common even though glycosuria is present

Urine Volume. In untreated and symptomatic diabetes the twenty four hour urine volume characteristically exceeds the average normal of 1500 cc In fact, the quantities may reach several gallons The great increase in the volume of urine gives but little index of the severity of the diabetes but, in general, the greater the volume the greater is the amount of sugar present Occasionally the polyuria is so great that amounts totaling more than 50 per cent of the body weight may be voided in twenty four hours Control of the diabetes restores the rate of urine excretion to normal

Ketonuria. Ketonuria is the first recognizable sign of ketosis though it is of little importance in the diagnosis of diabetes It results when, from

a lack of insulin, the metabolism of carbohydrate is reduced, the metabolism of fat is accentuated and ketones are produced in greater than normal quantities. Ketones are also derived from certain amino acids. Ketonuria occurs in a mild form in healthy nondiabetic subjects whose food intake, especially the carbohydrate, is greatly curtailed. Ketonuria, caused by diabetes, is common without other evidence of ketosis. This was an especially common finding in the pre-insulin era when diets high in fat and low in carbohydrate content were the rule. A considerable quantity of ketones may be excreted in the urine without their accumulation in the blood or without a reduction of the carbon dioxide combining power. Failing appropriate treatment, however, the rate of the production of ketone eventually exceeds the rate at which they can be excreted. It is then that qualitative reactions for acetone and diacetic acid in the plasma, or serum become positive and it is then that the acetone odor appears on the breath. An extremely rare exception to this rule is seen when, with renal disease, small amounts only of acetone appear in the urine when large quantities are retained in the blood.

The ketone bodies are acetone, diacetic acid and beta hydroxybutyric acid. Acetone and diacetic acid appear under similar conditions. Both are identified by a modified Rothera test,* or more convenient still the Ace test†.

An increasing loss of beta hydroxybutyric acid in the urine accompanies a deepening ketosis. In severe ketosis it is in this form that most of the ketones are lost, amounting to as much as 200 gm. in twenty four hours. The tests for acetone and diacetic acid in the urine are strongly positive before appreciable amounts of hydroxybutyric acid are excreted.

Ketonuria is a guide for further investigation. The amount of ketones excreted is of less immediate importance than the amount of these products which has accumulated in the tissues and in the blood. It has been shown that mild degrees of ketonuria may persist for months and years without apparent harm, whereas, a 4 plus reaction for ketones in the blood from a patient who also has glycosuria is ample evidence to make a diagnosis of diabetic coma.

Qualitative Tests for Acetone. (a) THE 'ACETEST' TEST. This test for acetone is a simple and reliable test which merely involves the adding of a drop of freshly voided urine or freshly secured sample of plasma or

* Bedside test for plasma acetone and diacetic acid (Rothera-Wisbart). Two drops of plasma or serum are placed in a Wassermann tube and supersaturated with ammonium sulfate crystals and shaken. Two drops of approximately 5 per cent sodium nitroprusside solution are added and shaken. Two drops of ammonia water are added and shaken. Allow to stand for three minutes.

Interpretation: Permanganate color — trace of plasma acetone

Light blue — no ferate

Deep blue or almost black — heavy reaction for plasma acetone

† Acetest reagent tablets are manufactured by Ames Co. Inc. Elkhart, Ind.

serum to a tablet which contains amino acetic acid, disodium phosphate and sodium nitroprusside. The color of the tablet is noted after thirty seconds have elapsed. Interpretation of the test

White or cream color	negative test
Purple tint	1 plus reaction
Lavender	2 plus reaction
Moderate purple	3 plus reaction
Deep purple	4 plus reaction

(b) **ROTHERA'S TEST** * To 5 or 10 cc of urine add about 1 gram of ammonium sulfate and 2 or 3 drops of fresh concentrated sodium nitroprusside solution and overlay with strong ammonia. A reddish purple ring shows the presence of acetone.

(c) **ACETONE TEST (DENCO)** This simple and accurate test for acetone is executed by depositing on a dry white paper sufficient of the Acetone Test (Denco) reagent—containing sodium bicarbonate, ammonium sulfate and sodium nitroprusside in anhydrous form—to cover one third of a dime and by moistening this *entire amount* of powder with 2 or 3 drops of urine to be tested. In the presence of acetone a shade of purple will develop within thirty seconds, a trace of acetone yields a light lavender color and with increasing amounts the color will be darker, a dark blue indicating a 4 plus reaction. In the absence of acetone a grayish yellow color is the result.

We use this test routinely in examining the urine and the blood plasma or serum, for acetone.

(d) **QUALITATIVE TEST FOR DIACETIC ACID IN THE URINE (GERHARD'S TEST)** To a few cubic centimeters of the urine add 10 per cent aqueous solution of ferric chloride, drop by drop, until the phosphates are precipitated, filter and add more of the ferric chloride. If diacetic acid is present, the urine assumes a Bordeaux red color. Clinically, we do not employ the test for diacetic acid but rely on the tests for acetone as indication of the degree of ketonuria.

THE BLOOD

Sugar Content. Hyperglycemia is the most decisive indication of diabetes. Without it the diagnosis cannot be made with certainty. A concentration of sugar in a specimen of venous blood, taken after an eight to fourteen hour fast, in excess of 130 mg per 100 cc, or a value exceeding 170 mg after a hearty meal is usually due to diabetes. There is practically no difference in the sugar concentration in venous and arterial (capillary) blood in the postabsorptive (fasting) state. After a meal, how

* Todd and Sanford. *Clinical Diagnosis by Laboratory Methods*, 11th Ed., W. B. Saunders Company, Philadelphia 1943.

ever, and in the normal person the arterial blood sugar level is from 20 to 50 mg per 100 cc higher than that in the venous blood. This difference represents utilization of sugar by the tissues and the difference is reduced in untreated diabetes and the normal variation is restored by adequate treatment.

A diagnosis of diabetes should never be made on the basis of a single blood analysis unless the hyperglycemia is accompanied by glycosuria and characteristic symptoms. The most certain criteria of diagnosis are repeatedly elevated fasting blood sugar values and glycosuria. It is significant that in the patient with an untreated but mild diabetes glycosuria tends to subside toward morning—at the end of the longest period without food. It is then also that the blood sugar level is the lowest in the twenty-four hours.

Sugar is present in the blood of normal persons in concentrations varying from 70 to 110 mg per 100 cc fasting (according to the Folin Wu method). There are slight differences in the values according to the method of determination employed but clinically these differences are insignificant. The blood sugar levels in the average untreated diabetic patient without acute complications range between 180 and 300 mg per 100 cc (Folin Wu method).

The hyperglycemia and glycosuria of diabetes behave in a characteristic manner. Liberal additions to the carbohydrate and total caloric intake tend to increase their severity, while restricted carbohydrate and total food allowance have the opposite effect.

Hyperglycemia may be present for only short periods, two to four hours after each meal with normal fasting values in patients having mild diabetes. The likelihood of identifying these mild cases is enhanced by taking the blood specimen for determination of the sugar value two hours after the biggest meal of the day. Values in excess of 170 mg per 100 cc and an accompanying glycosuria make the diagnosis obvious.

The degree of hyperglycemia alone is not an accurate index of the severity of the diabetes. An untreated obese patient may have a blood sugar level of 500 mg or more per 100 cc and yet the mildness of the diabetes is apparent when the hyperglycemia is promptly corrected by merely restricting the total food intake. It is a reliable rule to consider that every *untreated* overweight diabetic patient has a *mild* diabetes despite the degree of the hyperglycemia that is found. In contrast the underweight patient with untreated diabetes has a *severe* diabetes though the blood sugar level may not exceed 250 mg per 100 cc. To restore the underweight patient to good health a gain in weight is imperative. This end is achieved only by a liberal food intake and insulin therapy. *To repeat the level of the blood sugar is not a reliable index of the severity of the diabetes.* The degree of hyperglycemia in the light of the relationship of the patient's weight with that of the normal is a more reliable guide. *The fat diabetic patient has a*

mild diabetes and the lean diabetic patient with a persistent fasting hyperglycemia has a severe diabetes. It is well, in most instances, to delay giving an opinion on the severity of the diabetes in underweight patients until repeated blood sugar values are known and their response to appropriate treatment is observed.

Other departures from the normal composition of the blood (Table 10) are not of special value in arriving at a diagnosis of diabetes. They are for the most part, observed during complications of this disorder and will be dealt with under the respective complications. We refer to alterations in the hemoglobin, the urea nitrogen, concentration in the blood plasma acetone, carbon dioxide combining power, plasma or serum chlorides, the blood volume as seen in ketosis, and cholesterol and fatty acid values.

TABLE 10]

ALTERATIONS IN THE COMPOSITION OF BLOOD ASSOCIATED WITH DIABETES MELLITUS†

CONSTITUENT	NORMAL RANGE	IN UNTREATED DIABETES
		n ketosis
		n ketosis
		n ketosis
		n ketosis
		ketosis
Glucose (mg / 100 ml)	90 - 140*	Increased in ketosis
Potassium—as K (mEq / L)	3.8 - 5.3*	Increased in untreated ketosis
—as mg / 100 ml	11.8 - 16.8	Decreased after onset of treatment for ketosis
Sodium—as Na (mEq / L)	133 - 136	Decreased in ketosis
—as Na (mg / 100 ml)	307 - 316	Decreased in ketosis
Sugar—as total reducing substance arterial whole blood ** (mg / 100 ml)	80 - 110*	Increased
venous (mg / 100 ml)	70 - 100*	Increased
Cholesterol—Total (mg / 100 ml)	150 - 190*	Increased
Fatty acids—Total (mg / 100 ml)	290 - 420	Increased
Lipid Phosphorus—Lecithin (mg / 100 ml)	12 - 14	Increased
Total acetone bodies (as acetone) (mg / 100 ml)	1.3 - 2.6	Increased in ketosis
Acetone—qualitative test on plasma	negative	++++ in diabetic coma

* Extracted from Sunderman and Boerner's Normal Values in Clinical Medicine W B Saunders Company, Philadelphia 1950

** Blood is taken from the finger tip or from the lobe of the ear

† The values are those obtained on plasma or serum taken under fasting conditions unless otherwise indicated

Note: In the clinical management of diabetes the common studies are those of blood sugar, cholesterol, CO₂ and plasma acetone

CHAPTER XI

Symptomatology, Physical Signs and Diagnosis of Diabetes

A. SYMPTOMATOLOGY

The symptoms of diabetes may be classified into three groups (a) those of uncomplicated diabetes, and diabetes with (b) acute complications and (c) chronic complications

(a) **Uncomplicated Diabetes.** The symptoms associated with uncomplicated diabetes are fatigue, polyuria, polydipsia, polyphagia, loss of weight and pruritus. The onset of symptoms, in presumably uncomplicated diabetes, is usually insidious but it may be abrupt—so abrupt indeed that the date of onset can be clearly recollected. This latter manner of onset is most frequently encountered in the young diabetic patient.

(b) **Acute Complications.** Rapid intensification of the symptoms of uncomplicated diabetes plus an *acute infection* e.g., carbuncle, furuncle, infection of the respiratory tract and the symptoms that characteristically develop as a result of the respective infections. Failing corrective measures, anorexia, nausea and vomiting, dryness of the mouth, drowsiness, abdominal pain and coma, all being symptoms of *diabetic ketosis*, may develop gradually over several days with no other apparent complication, but usually they develop rapidly—in a matter of hours—and an acute precipitating complication is usually detectable. An *occlusion of a coronary artery* with the characteristic sub-sternal pain is among the common acute complications of diabetes.

(c) **Chronic Complications.** The symptoms associated with, and due to, chronic complications are, for the most part, indicative of degenerative changes and these are largely of the vascular system.

Dimness of vision, sudden or gradual, of mild or severe grade, and, less frequently, headaches are symptoms which suggest *diabetic retinitis*, *cataracts* and *glaucoma*.

Sub-sternal pain or numbness, or pain in the left shoulder and arm precipitated by exercise, and promptly relieved by nitroglycerin therapy, indicate *insufficiency of the coronary circulation*.

Weakness, nocturia, swelling of the ankles with hypertension albuminuria and retinitis are signs of *intercapillary glomerulosclerosis*

Pain along the course of a nerve, burning, numbness, tingling aches and bizarre widespread pains, particularly in the legs and feet and occurring at night, paralysis, tabetic manifestations with disturbed sensation in the feet, disturbed efficiency in sweating and impotence occur in *diabetic neuropathy*

Irregular menses or amenorrhea, relative sterility, and various difficulties attending pregnancy in the diabetic attend the *hormonal disturbances* of diabetes

Pain in the calf muscles on exertion which is relieved by rest (intermittent claudication), coldness and cramps in the extremities, paresthesias with development of cyanosis in the feet when placed in the dependent position and with pronounced pallor when elevated, with or without evidences of gangrene, signify *advanced peripheral vascular disease*

The complications of diabetes and their varied symptomatology are dealt with in Chapter V. The more important complications and the symptoms to which they give rise are presented here for the sake of completeness but also because the only presenting symptom that may lead to the detection of the diabetes is often a symptom of some complication

Special Consideration of Symptoms

Symptoms may suggest a diagnosis of diabetes but nothing more. On the other hand, the finding of glycosuria, an initial step toward a diagnosis is not infrequent in the absence of classical symptoms

The varied symptomatology of diabetes in a typical case is at once indicative of some systemic disorder. General weakness, loss of weight, excessive appetite and thirst, the frequent passing of large quantities of urine without discomfort, rising at night to void, pruritus (which in the female occurs particularly about the vulva), and backache are the most common symptoms of uncontrolled and uncomplicated diabetes. Loss of libido with impotence in the male is less common than the foregoing classic symptoms but is more frequent than is generally supposed. Direct questioning of patients may be required before this complaint is elicited.

It has been estimated that as high as 12 per cent of patients having diabetes have no symptoms of this disorder. This observation is based on the finding of glycosuria in applicants for insurance and those undergoing routine health examinations. There is no doubt that many persons who are free from symptoms have a mild diabetes of which they are ignorant. We are incredulous, however, of the value of figures based on applicants for life insurance who state that they have no symptoms.

General Weakness This may be the only symptom of diabetes. It has been the most common presenting complaint of our diabetic patients. This symptom, common to so many debilitating diseases gives little indication of the nature of the underlying disorder. It is a symptom, however, that

deserves serious consideration and it is a good practice to investigate thoroughly each patient who complains of it

Loss of Body Weight A rapid loss of body weight in the afebrile patient, especially in the young diabetic patient, is common. This symptom is readily accounted for. Glycosuria occurring in amounts varying from mere traces to as much as 15 per cent accounts for a good portion of the loss of weight. Glycosuria causes a peculiar form of starvation but accounts for the seeming paradox which exists when, with increased appetite for food, the intake greatly exceeds that of the normal and yet a loss of weight continues. There is an excessive breakdown of protein as indicated by the abnormally large quantities of nitrogen excreted in the urine. Loss of weight is due, in part also, to the loss of body water by the diuresis resulting from the effect which the high concentration of sugar in the blood exerts on the renal tubular epithelium. Further loss in weight is encountered in the presence of ketosis in which an increased degree of dehydration, and loss of nourishment, in the form of ketones, are additional factors. This feature is dealt with in the section on complications.

Great importance attaches to body weight and its changes in diabetes. A person with untreated and uncontrolled diabetes may lose weight while partaking of an unrestricted diet. During this process the diabetes tends to become more severe, hence, loss of weight in this manner is injurious. This is true even in the case of the obese patient because it leaves less weight to be reduced by a method which improves and controls the diabetes. This latter and beneficial method of reducing weight is brought about by curtailing the patient's total food intake—exactly as one would reduce an obese nondiabetic patient. This restriction lessens the immediate demand on the islet function of the pancreas and at the same time consolidates this gain, since it reduces the total metabolism by virtue of the reduced body weight which ensues. Ridding monotony in repetition concerning one of the most important aspects of clinical diabetes we restate: A loss of weight, i. e. a decrease in total metabolism secured by the restriction of the total diet, decreases the food loss, gives the pancreas functional rest, affords the overweight patient with uncontrolled diabetes a remarkable improvement in carbohydrate and total food tolerance and brings the diabetes under control without the administration of insulin.

A loss of weight due to the activity of the diabetes, whether due to ignorance or willful neglect, destroys food tolerance, the diabetes becomes more severe, and the need for insulin increases. An obese patient who becomes underweight because of the activity of the diabetes loses all of the advantages that go with a reduction in weight by appropriate treatment, and the necessity of using insulin indefinitely is usually inescapable. We hope this is clear. It is of vital importance. It represents one of the fundamental considerations of diabetes, the understanding of which we owe to Dr. Frederick M. Allen.

Excessive Appetite and Thirst. These symptoms occur in direct relation to the amount of glycosuria and the polyuria until ketosis intervenes. As ketosis develops anorexia replaces the polyphagia. Excessive appetite is a compensatory effort to replace lost nourishment, polydipsia, to replace lost fluids. The thirst and the frequent voiding of large amounts of urine are among the most common symptoms of diabetes occurring in about three quarters of all cases. It is in this group of patients that back ache is common. This symptom can be reproduced in a normal person by having him drink large quantities of water. Distention of the renal capsule by increased activity of the kidneys with greater than usual volumes of fluid passing through them apparently is responsible.

The physician who recognizes diabetes early does his patient a great service. No reliance is to be placed on the absence of symptoms. One has but to consider how much so many patients owe to chance examinations for other disorders, routine or insurance examinations, to realize this. Diabetic patients who are free from symptoms are not immune to complications, nor is the diabetes innocent in such cases.

Complications of diabetes often prompt the patient to seek treatment. The discovery of diabetes, of the presence of which the patient may be entirely ignorant, is often made on such consultations.

B PHYSICAL FINDINGS IN DIABETES

Many diabetic patients are obese but many have no physical evidence of the diabetes from which they suffer. However, the more carefully the examination is made, the more often will the search be rewarded by the discovery of abnormalities which, when correlated with the symptoms, are found to be more or less characteristic. We refer especially to the *fatigued appearance*, the *looseness and wrinkling of the skin* observed in patients who have *lost weight*, and to *dryness of the skin* in those patients who suffer from excessive thirst and polyuria. There is a mild degree of *pallor* of the skin of the face in many diabetic patients. This is particularly noticeable in those who are overweight, are past middle age, and who have advanced disease of the arteries. This may be attributable to the elevation of the blood lipid concentrations, but in most instances it is probably due to vascular disease. It is especially common in patients suffering from disease of the coronary arteries. In the young patients, particularly females, taking large amounts of insulin, the skin may have a waxy transparency with a smoothing out of wrinkles of the face. This has been referred to as an 'insulin face'. It is noticeable shortly after insulin therapy is begun and is due to water retention in the skin. This condition tends to disappear when the diabetes is controlled over a period of months. We can recall, however, several young women in which this state remained unchanged for several years.

Other skin disorders may occur as a result of the diabetes namely, *xanthelasma palpebrarum* and, rarely, *xanthoma diabeticorum* and *necrobiosis lipoidica diabeticorum*.

Though all shades of health from the robust, normal appearing diabetic patient to one critically ill with ketosis are observed, it is well to emphasize that most physical abnormalities observed in these patients are due to complications of diabetes. The untreated diabetic patient is especially susceptible to gingivitis, *pyorrhea alveolaris* and to *staphylococcal* infections e.g., furuncles, carbuncles and bacteremia. He is more prone than the non

diabetic to tuberculosis. This complication is most

common in the diabetic. In a study of 1000 diabetic patients, Boucot,

Cooper and Richardson² found tuberculosis to be twice as common in 3106 diabetic patients surveyed as in a similar nondiabetic group.

The degenerative changes are readily detected on physical examination especially cataracts, diabetic retinitis and generalized disease of the arteries. Coldness of the extremities, cyanosis of the feet in the dependent position and a cadaveric pallor when they are elevated, gangrene of the toes, heel or other parts of the feet occur as a result of extensive changes in the arteries. Irritation of the skin may be generalized but occurs most frequently about the genitals as a result of pruritus, which is common, as are *epidermophyton* infections. The fungus infections involve the feet, between the toes most frequently but may be found elsewhere on the body.

The physical signs of diabetic coma are considered in detail elsewhere but because signs of this complication should be looked for in every acutely ill diabetic patient they are summarized here as follows: marked dehydration, an odor of acetone on the breath, "air hunger" (Kussmaul's respiration), reduced intra ocular tension, dry skin and mucous membranes, low blood pressure, hypothermia, rapid pulse, signs of pleurisy (uncommon), abdominal tenderness with varying degrees of rigidity, and coldness of the extremities.

C. LABORATORY STUDIES IN THE DIAGNOSIS OF DIABETES

The diagnosis of diabetes rests finally on laboratory data, the most important of which are

- 1 Glycosuria—occurring concomitant with a hyperglycemia
- 2 Hyperglycemia
- 3 Special tests for doubtful cases
 - a Effect of a meal containing 100 gm. of carbohydrate on the concentration of sugar in the blood
 - b Standard glucose tolerance test

consider this simple test to be more reliable than the one hour, two dose glucose tolerance test, it is inexpensive and it can be readily carried out in a physician's office with a minimum expenditure of time. At least as a preliminary study this test has merit and when glucose tolerance tests may be impracticable we recommend it as a satisfactory substitute in many cases in clinical practice.

The patient prepares for the test by partaking of a normal diet which will include at least 300 gm of carbohydrate daily for at least three days prior to taking the test meal.

The test meal (see Table 11) is taken in place of the regular breakfast and venous blood (5 cc) for a sugar determination is taken two hours after the meal is finished. If the value (venous blood sugar, Folin Wu method) exceeds 170 mg per 100 cc and glycosuria is present it is practically certain that diabetes is the cause. If the value is below 130 mg, however, it

TABLE 11
TEST MEAL CONTAINING 100 GRAMS OF CARBOHYDRATE

		PROTEIN GM	FAT GM	CARBOHY- DRATE GM
Banana	155 grams (1 medium)	1.5	—	31.1
Shredded wheat	30 grams (1 1/2 cup)	3.3	0.3	22.5
Milk	210 grams (1 cup)	7.2	9.6	12.0
Bread (white)	60 grams (2 slices)	5.4	0.6	31.8
Butter	10 grams (2 teaspoonfuls)	—	8.5	
Total calories	612	17.4	19.0	100.4

is unlikely that diabetes is present. To add to the certainty of the diagnosis a glucose tolerance test (see p. 60) may be desirable.

A final diagnosis should not be made on the basis of only one determination of the blood sugar. Specimens can become misplaced and errors can be made. Also, transitory glycosuria and hyperglycemia, nondiabetic in nature, are not uncommon in cases of head injuries, intracranial infections or vascular accidents, thyrotoxicosis, hyperpituitarism, excessive activity of adrenal hormones—medullary and cortical—emotional disturbances, some diseases of the liver, during anesthesia, asphyxia and poisoning from chemicals.

Some latitude is permissible in establishing the diagnosis of diabetes in the thyrotoxic patient. We allow a moderate degree of hyperglycemia, 20 mg per 100 cc above that of the non thyrotoxic patient, before considering it diagnostic of diabetes. Even then, this diagnosis should be tentative, in the borderline cases, until the thyrotoxicosis is corrected and the usual methods of evaluating the diabetes are applicable.

(b) Standard Glucose Tolerance Test. It is in diabetes mellitus

that gross alterations in carbohydrate tolerance are most frequently observed. It is in the detection of this disease in its mildest states that use is made of the fact that normal individuals can ingest considerable quantities of carbohydrate with but trifling changes in the concentration of sugar in

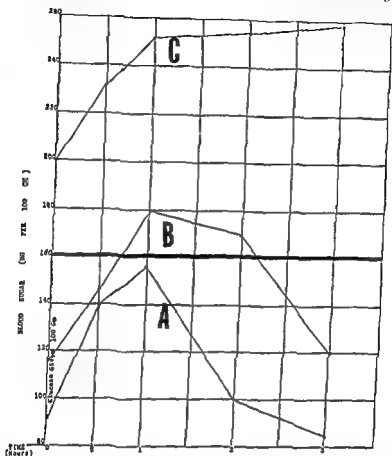


Fig 14 Three glucose tolerance curves. *A* depicts the normal glycemic response to the oral administration of 100 gm of glucose. The rise in the blood sugar level is rapid but a normal value is restored in two hours. In *B* the glycemic response is slower and normal values are not restored until the third hour as is found in mild diabetes. *C* depicts the fasting hyperglycemia and the continued increase in the blood sugar level even at the third hour as seen in severe diabetes. Glycosuria usually occurs when the blood sugar level is maintained for varying periods above 160 mg per 100 cc as depicted by the heavy black line.

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the presence or absence of diabetes. The value of this test lies in its diagnostic aid and not as an indicator of the severity of the diabetes. If the patient is underweight and has a high fasting blood sugar value the diabetes is almost certain to be severe and in these cases results similar to those depicted in Curve C, Figure 14, would be found, i.e., a hyperglycemic fasting blood sugar value with continued increases in the degree of hyperglycemia throughout the three hours subsequent to the oral administration of 100 grams of glucose. We wish to emphasize that in clinical practice a confirmed fasting blood sugar value of 130 mg per 100 cc or higher, with glycosuria would establish the diagnosis and make a glucose tolerance test unnecessary. The curve (C) is presented as an illustration of the values encountered in such a case and not as a recommendation that a glucose tolerance test be done when the diagnosis is obvious without it. Glucose tolerance tests in such cases are needless. In spite of this, the practice of performing these tests on patients obviously diabetic is widespread. This practice is particularly pernicious in the federal and military hospitals.

Indications. In general the glucose tolerance test is indicated when the diagnosis of diabetes or its exclusion, cannot be clearly made without it. Individuals for whom the test is employed will fall into one, or a combination of the following categories, namely, those having

a *History of glycosuria*—applicants for life insurance are the most frequent subjects for a glucose tolerance test under the circumstance of having a history of glycosuria.

b *Family history of diabetes*—for many reasons it is important for one with a family history of diabetes to establish the presence or absence of this disorder. Contemplation of marriage, the selection of occupation, and the adoption of preventive or palliative measures are examples of these reasons.

c *Transitory glycosuria and hyperglycemia during other complications*, e.g., pregnancy, hyperthyroidism, hepatitis, staphylococcal infections—particularly furuncles and carbuncles—and following a starvation regimen. Follow up tolerance tests are of special value in this group.

d *Glycosuria without hyperglycemia* as occurs in renal glycosuria, e.g., nephrosis and in some cases of pregnancy and of thyrotoxicosis. The value of such a study is emphasized when one recalls seeing patients who have been needlessly and ineffectively dieting and taking insulin when the disorder was one of renal glycosuria.

Contraindications. It is important when practicable, to perform this test in the absence of conditions other than a possible diabetes that would influence the tolerance unfavorably. For this reason the glucose tolerance test for the detection of diabetes is contraindicated during the course of infections, hepatic disturbances and dietary restrictions especially a starvation regimen or a low carbohydrate diet or a high fat diet low in carbohydrate content which though they do not alter the true capacity of

pancreatic islet cell function, do exhibit temporary alterations which are adaptations to a reduced demand for insulin (Allen). In patients with thyrotoxicosis an additional 20 mg of sugar per 100 cc of blood, above that usually considered as indicative of diabetes, is allowed.

The glucose solution occasionally causes nausea. This delays absorption and distorts the blood sugar concentration curve, hence, if the curve does not conform to that for a normal tolerance in the event of nausea, the test should be repeated after a lapse of seven to ten days. Tests done before a week has elapsed may mislead, as in mild diabetes a rapid succession of tests tend to show a progressive improvement in the tolerance for glucose. Also, active exercise during the course of the test will have a similar effect. Contrariwise, prolonged rest in bed tends to reduce the tolerance for glucose and permits slightly higher curves than are obtained when the subjects are ambulatory.

Technic of Standard Glucose Tolerance Test The patient reports in the morning having had a daily intake of at least 300 gm of carbohydrate for at least three days immediately prior to the test but having had no food since the previous evening. The bladder is emptied, a sample of venous blood (5 cc) for sugar determination is taken and 100 gm of glucose, dissolved in 300 cc of water and flavored with the juice of a lemon, is given by mouth. Specimens of blood and urine for sugar determinations are secured one half hour later, and at one, two and three hours.

Interpretation Two values in the curve depicting the various concentrations of sugar in the blood are of outstanding importance, as it is upon them that the real value of the test depends. They are (a) *the fasting blood sugar value* and (b) *the value obtained two hours after the ingestion of 100 gm of glucose (or 1.75 gm per kilogram of body weight in the case of a child)*.

FASTING VENOUS BLOOD SUGAR The normal range of the fasting blood sugar concentration is between 70 and 110 mg per 100 cc. Values in excess of 130 mg are indicative of diabetes unless proved otherwise.

THE TWO HOUR BLOOD SUGAR VALUE The normal individual is able to restore the blood sugar level to 120 mg or lower two hours after the ingestion of the glucose. A more liberal interpretation is permissible in the event of one of the complicating conditions (see p 84), which mildly depress the carbohydrate tolerance. In these instances two hour values up to 150 mg are considered nondiabetic if the three-hour value is below 120 mg per 100 cc. Such curves are common in cases of thyrotoxicosis, the correction of which restores normal responses to glucose tolerance tests and in so doing justifies the lenient interpretation in such cases.

THE PEAK VALUES The maximum concentration of sugar in the blood normally is found thirty or sixty minutes after the ingestion of glucose. Some authorities believe that if the peak value exceeds 170 mg per 100

cc it is indicative of diabetes. We give little heed to the peak of the curve even if it exceeds 200 or 220 mg per 100 cc providing the two hour value is restored to 120 mg or below. A blood sugar regulating system which, between the one-hour and two hour intervals, can eradicate such a degree of hyperglycemia is, most probably, not lacking in insulin. Unusually high peaks at one half and one hour are more likely to be due to an unusually rapid rate of absorption, as is known to occur in cases of a functioning gastro enterostomy and of thyrotoxicosis.

Barring conditioning influences already mentioned a *normal curve* reveals a fasting value below 120 mg and a two hour value at or below 120 mg per 100 cc. *Tolerance curves are indicative of diabetes*, if the clinical evaluation is in keeping with the diagnosis, and if the fasting blood sugar exceeds 120 mg and if the two-hour value exceeds 130 mg per 100 cc. It is agreed that the fasting blood sugar may be normal, and indeed it usually is, in cases in which the glucose tolerance test is used properly. This being the case *the value which is of utmost importance is that obtained at the end of two hours*. Indeed, in the majority of cases, the test and interpretation may be simplified and the expense reduced by doing only one blood sugar determination—two hours after the glucose has been taken. This is assuming that previous fasting blood sugar values have been normal. Barring again, the conditioning influences mentioned on page 84, a two hour value above 130 mg is indicative of diabetes.

Glycosuria may influence the type of curve. Large quantities of sugar in the urine, occurring concomitantly with blood sugar values on the borderline, would weigh in favor of a diagnosis of diabetes in the belief that had no, or very little glycosuria resulted the concentration of sugar in the blood would have been higher.

Urine, collected simultaneously with the collection of each blood sample, permits a study of the relationship of glycosuria to the degree of glycemia as well as some evaluation of the renal threshold.

The excretion of glucose in the urine depends upon (a) the concentration of sugar in the arterial blood reaching the glomeruli of the kidneys, (b) the rate at which the glomeruli filter the sugar out of the blood and (c) the rate at which the filtered glucose is reabsorbed by the renal tubules.

The renal threshold is usually considered in terms of the concentration of sugar in venous blood which is an unreliable index of the concentration of arterial blood reaching the renal glomeruli for at least several hours after the ingestion of food. The varying differences between the arterial and venous blood sugar concentrations during a glucose tolerance test are presented in Figure 15. These differences should be considered in evaluating renal glycosuria if there is to be clear thinking of the physiologic processes in operation.

Some authorities, and notably Lawrence,² prefer using capillary blood

to venous blood for sugar determinations. The former is subject to a greater range of concentration and is likely to be misleading to one inexperienced with the method.

The greater stability of the venous blood sugar values over capillary blood would appear to make the former the more reliable for clinical purposes.

Miscellaneous States Affecting Tolerance Test The degree to which carbohydrate tolerance is depressed in a multitude of clinical disorders

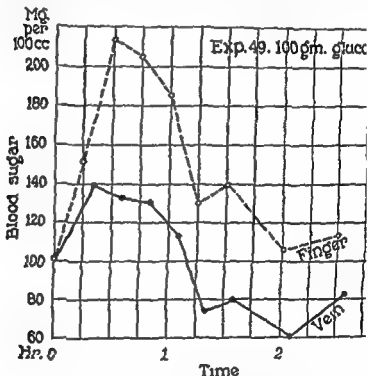


Fig. 15 Sugar of venous and finger blood after ingestion of glucose (From G. L. J. Biol. Chem. Vol. 55)

slight as to cause no conclusion in differentiating the usual case from that of diabetes. These changes are noted in rheumatoid arthritis, semilunar diseases, cardiac decompensation, arterial hypertension, nephropathy, pregnancy, obesity, apoplexy, ulcerative colitis, cirrhosis of the liver, cholecystitis and bronchial asthma. It can be gathered from the foregoing remarks that every diabetic patient when suitably studied will exhibit an elevated and prolonged glucose tolerance curve but that every high and prolonged curve is not indicative of diabetes. When the results are equivocal a subsequent test, or tests, are indicated. If employed wisely

interpreted in the light of good clinical judgment, glucose tolerance tests will rarely mislead.

(c) **The One Hour, Two-Dose Glucose Tolerance Test** (Exton Rose) This test has not been found in our experience, to be as reliable an index of disturbed carbohydrate tolerance as the foregoing standard glucose tolerance test. It is convenient in that it is simple to perform, requires

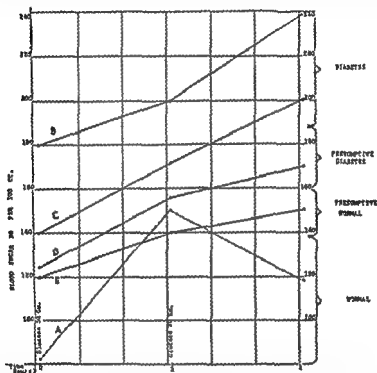


Fig. 16 Results of the one-hour two-dose glucose tolerance test (Exton Rose procedure)

Note A the normal curve the rapid rise and prompt fall of the blood sugar level B and C characteristic of diabetes with the continued increase in the sugar concentration with fasting values above normal. Curve D represents presumptive diabetes and curve E presumptive normal both are nondiagnostic.

fewer venipunctures than the three hour glucose tolerance test and is completed in one hour—a desirable feature in office practice. The results are dependable if the blood sugar values clearly indicate that diabetes is present (see curves B and C, Figure 16), or if they clearly signify a normal tolerance as indicated in curve A. It is noted, however, that there is a broad zone in which the interpretation can only indicate a presumptive diagnosis.

of diabetes when the blood sugar values are in the upper portion of the zone, or the presumption that diabetes is not present if the values are somewhat lower. In practice, a test is needed that will be clearly positive in its indications and especially in those cases in which the one hour test is apt to leave one with a presumptive diagnosis only. The high incidence of inconclusiveness which attends the use of this test in doubtful cases has led us to abandon it in preference to the standard glucose tolerance test. Furthermore, the Exton Rose test has been based on a misconception concerning the underlying physiologic processes which account for the types of curves obtained.⁴ It is agreed that the maximum rate of absorption of glucose from the gastro intestinal tract is 0.85 gm per kilo of body weight per hour or about 60 gm per hour for the average sized man.⁵ There is evidence that the maximum absorption is carried on at a slower rate than this, namely, 43 gm per hour.⁶ This being so, a one hour study cannot possibly give an accurate measure of the patient's ability to dispose of 100 gm of glucose, much of which is still in the intestinal tract at the end of this period.

Furthermore, it is not the second dose of glucose which causes the blood sugar values to fall in the second half hour of the test but rather the accelerated utilization of sugar by the tissues and cessation of the production of sugar from glycogen by the hepatic processes which are set in motion when the blood sugar is initially increased. This mechanism once in action, under normal conditions, continues until the blood sugar is slightly subnormal. The blood sugar concentration begins to fall from its peak when the rate of sugar utilization surpasses the rate of absorption from the gastro intestinal tract and this occurs even while maximum absorption is taking place and is not affected by an additional dose of glucose given one half hour after the initial dose. Minor changes in the rate of absorption and not necessarily in the rate of utilization, may determine whether the higher concentration of sugar in the blood occurs one half hour or one hour after the administration of the initial dose of glucose. This is also true when the standard three hour glucose tolerance test is used but, in this case, the longer period permits a greater degree of correction than is possible in one hour.

It is for the foregoing reasons that the Exton Rose glucose tolerance test is not recommended for the detection of diabetes in doubtful cases.

Technic The patient reports before breakfast having had a daily non restricted diet with a carbohydrate intake of at least 300 gm for three days preceding the test. One hundred grams of glucose are dissolved in 650 cc of water. This is flavored with lemon and divided into two equal parts. The test is conducted after an overnight fast.

- 1 The bladder is emptied.

- 2 A sample of venous blood (5 cc) is taken and immediately there

after one of the portions of glucose in solution (50 gm of glucose) is given by mouth

3 After a thirty minute interval a second sample of blood is taken, a urine specimen secured and the remaining glucose (50 gm) solution is given

4 After another thirty minute interval specimens of blood and urine are obtained

The sugar concentration in each specimen of blood and the amount of sugar if any in the urine are determined

Normal Tolerance Curve 1 The fasting blood sugar level is below 120 mg per 100 cc

2 The one-hour level does not exceed 160 mg per 100 cc

3 The blood sugar level is lower at the end of one hour than at the end of the first half hour

Tolerance Curves Indicating Diabetes 1 The fasting blood sugar value may be normal or in excess of 120 mg per 100 cc

2 A continued increase of more than 25 mg in the sugar level during the second half hour

3 A one-hour blood sugar value in excess of 160 mg per 100 cc

(d) *Intravenous Glucose Tolerance Test* This test is not recommended for general clinical use. However in the unusual case when it is important to circumvent abnormalities of absorption of glucose from the intestine, such as occurs in thyrotoxicosis, hypothyroidism and gastroenterostomy subjects this test may be of value

Technic Glucose 0.5 gm per kilogram of body weight, is given intravenously as a 20 per cent solution in distilled water at a uniform rate over a period of one half hour. Blood (5 cc) is withdrawn for sugar determination before the infusion is begun, at one half hour, at one hour and hourly thereafter until four hours have elapsed from the time the infusion was begun

Interpretation *Normal Result* the initial blood sugar level is normal the concentration of sugar in the blood does not exceed 0.25 per cent upon completion of the infusion and the level thereafter falls steadily, going below the initial level at two hours with a return to the pre-injection level or thereabouts between the third and fourth hours

In diabetes the blood sugar does not return to normal (below 120 mg per 100 cc) within two hours of commencing the infusion

Differential Diagnosis

Diabetes may be confused with other disorders which cause glycosuria and hyperglycemia. The life of an unconscious patient who has glycosuria and a hyperglycemia as the result of an intracranial hemorrhage may be jeopardized if careful investigation fails to reveal the real illness. Should the condition be mistaken for diabetic ketosis and large amounts of insulin be given, the danger is obvious

Glycosuria. The presence in the urine of substances which reduce copper in solution to cuprous oxide may be mistaken for glucose. These are pentose, lactose, levulose, maltose, and rarely galactose, conjugated glycuronates, homogentisic acid, vitamin C and creatinine. The recognition of these various factors is dealt with on page 90. Glucose appearing in the urine of a nondiabetic patient is apt to be especially misleading. It occurs in *renal glycosuria* and *following intracranial injuries* and in *shock*.

Renal Glycosuria. Glucose appearing in the urine in the presence of a normal blood sugar concentration is known as renal glycosuria, referred to also as "benign glycosuria" and "diabetes innocens." Renal glycosuria is a symptomless and innocent condition requiring no treatment. It has to do with alterations in the renal threshold for glucose and represents a reduction in the ability of renal tubules to reabsorb sugar which has passed through the glomeruli. The blood sugar level above which glycosuria occurs is the so called *renal threshold* for glucose. If the venous blood sugar level in the normal individual is increased artificially, glycosuria occurs between

TABLE 13

THE RELATIONSHIP OF THE BLOOD SUGAR LEVEL AND THE SUGAR IN THE URINE IN A CASE OF RENAL GLYCOSURIA

1 P.M.	1 30 P.M.	2 P.M.	2 30 P.M.	3 P.M.
Blood Sugar Per cent 0.100	Urine Sugar Per cent 1.5	Blood Sugar Per cent 0.108	Urine Sugar Per cent 1.4	Blood Sugar Per cent 0.098

160 and 180 mg. per 100 cc. In long-standing diabetes the renal threshold is often higher, even as high as 250 mg. per 100 cc. On the other hand, in renal glycosuria glucose appears in the urine without any elevation of the blood sugar above the normal concentration (70 to 110 mg. per 100 cc.). This innocent disorder occurs in two forms. The one in which there is a constant loss of glucose in the urine the quantity of which is not altered by changes in the diet and only with great difficulty by giving insulin, and the other in which there is a temporary lowering of the renal threshold as observed during pregnancy and hyperthyroidism. Renal glycosuria is not a forerunner of diabetes. Experimentally this condition is produced by giving phlorizin to animals.

Importance is attached to renal glycosuria because of the danger of mistaking it for diabetes. The combination—diabetes and a low renal threshold for glucose—occurs occasionally.

Renal glycosuria is probable if, when the diet is restricted or when insulin is given, there is no decline in the amount of glycosuria. Furthermore, from day to day there is little change in the amount of glycosuria. These inconclusive observations are suggestive but it is only by parallel

examinations of the blood sugar level and the urine that the condition is clearly demonstrated

A simple method of identifying a renal glycosuria is as follows. The bladder is emptied and the urine is discarded, 11 oz (240 cc) of water is given, a sample of venous blood is taken, thirty minutes later a specimen of urine is obtained and at the end of another thirty minutes blood is again obtained. If both blood sugar values are normal (70 to 110 mg per 100 cc) and if there is a considerable amount of sugar in the urine collected at the midway period the diagnosis of a low renal threshold is confirmed. One may carry the test further by securing a second urine specimen and a third blood sugar value as illustrated in Table 12.

Pregnancy and the Renal Threshold. In 10 to 15 per cent of normal pregnant women there is a lowering of the renal threshold for sugar allowing glucose, not lactose as is generally supposed, to escape in the urine. Lactosuria is common during lactation but does not occur during gestation. Lactosuria and glycosuria may be observed simultaneously in the same patient. The renal threshold for glucose returns to normal after the lactation period has ended.

Hyperthyroidism. In hyperthyroidism it is not unusual to find a lowering of the renal threshold for glucose. The problem is not as simple however as that which occurs during pregnancy. These patients are apt

frequently is restored to normal by appropriate treatment of the hyperthyroidism. Unfortunately this is not always the case.

Nephrosis. The renal threshold for glucose is lowered in nephrosis. It is assumed that degenerative changes in the tubular epithelium impair the absorption of glucose from the glomerular filtrate. The associated clinical evidences of nephrosis remove any diagnostic difficulties.

Alimentary Glycosuria. It is believed by some that alimentary glycosuria represents a decreased renal threshold for sugar but that the threshold is sufficiently high to prevent continuous glycosuria and that sugar appears in the urine after extra "loads" of carbohydrate. This interpretation should be accepted with reserve and a careful study of the individual's carbohydrate tolerance should be made in each instance. So-called "alimentary glycosuria" may be due to a reduced renal threshold for sugar or to an increased permeability of the intestinal mucosa for sugar. Both causes are innocent. It should be suspected however until proven otherwise that the glycosuria is due to diabetes.

Diseases of the Hypophysis. Hyperglycemia and glycosuria indistinguishable from that occurring in uncomplicated diabetes, are common in acromegaly.

The diabetes which occurs as the result of changes in the hypophysis in the acromegalic patient doubtless has its origin in the excessive activity of the pituitary gland. The fact that irreparable changes take place in the pancreas as a result of these changes has been conclusively shown experimentally by Young.⁷

The important consideration is that acromegalic patients who have hyperglycemia and glycosuria have two disorders, acromegaly and diabetes, and should be treated accordingly.

Pituitary Basophilism (Cushing's disease) This disease, due to tumor growth of the basophilic cells of the anterior lobe of the pituitary gland also causes hyperglycemia and glycosuria. Here also at least two disorders—basophilism and diabetes—coexist. The diabetes is doubtless due indirectly to the changes in the hypophysis.

Diseases of the Adrenal Glands. Hyperglycemia and glycosuria may occur as the result of a tumor of the adrenal cortex. The diabetes is indistinguishable from chronic diabetes ordinarily seen except that it is cured by removal of the adrenal tumor. The clinical signs of tumor of the cortex of the adrenal gland are indistinguishable clinically from those of pituitary basophilism.

The subcutaneous intramuscular or intravenous injection of epinephrine (adrenalin), an extract of the adrenal medulla, provokes hyperglycemia and may cause glycosuria. This is a transitory effect lasting only a matter of minutes. It neither causes nor predisposes to diabetes. The hyperglycemic response is due to a liberation of glucose from the liver. The same mechanism, under control of the sympathetic nervous system, operates in shock, fear and anger, and permits unusual effort to resist threatened danger.

Intracranial Injury. Clinically glycosuria and hyperglycemia are common after intracranial trauma. This may result from violent accidents in which the base of the brain is injured and in event of intracranial hemorrhage as a result of injury or disease of the vascular system, or from injury caused by intracranial tumors and acute infectious processes.

Glycosuria of this type is in no way related to diabetes. It should be equally clear, however, that a patient having diabetes may suffer an intracranial injury and so glycosuria in such cases should not be dismissed lightly.

Melituria. Melituria is a term employed to include all sugars which may appear in abnormal amounts in the urine. Sugar being detected by the usual tests is likely to be glucose but it may be levulose, pentose, lactose—during lactation—or very rarely galactose, maltose, mannoheptulose—following the ingestion of avocados—and sucrose, which does not give a positive reaction for sugar with Benedict's test until hydrolyzed with hydrochloric acid. Sucrosuria is to be suspected when a urine free from albumin has a specific gravity above 1.035.

The clinical significance of the nondiabetic meliturias is, first, the dan-

ger that they may be regarded as being due to diabetes with the prospect of a lifetime of treatment. Second, that a reducing substance in the urine especially glucose in hyperthyroidism and during pregnancy and lactose during lactation, may be taken for granted as being due to the current complication and the possibility of a co-existing diabetes be overlooked, and third, all melurias are clinically benign and relatively innocent except the glycosuria due to diabetes and that uncommonly seen in extensive hepatocellular disease in which case the patient is seriously ill. Hence from the physician's and patient's points of view the problem resolves itself into a question: *Is this sugar in the urine due to diabetes or is it not?* Methods employed in making the diagnosis in problem cases are dealt with on page 77.

From the point of view of the scientist it may be important to identify the sugar, especially if it is not glucose and not due to diabetes. Clinically the meluria is of little importance if it is not diabetic in origin and if it does not lead to an incorrect diagnosis.

* For more detail on the subject of meluria the reader is referred to the works of Cantarow and Trumper: *Clinical Biochemistry* 4th Ed. W. B. Saunders Company Philadelphia. Also Marble A. C. *Met Clin N Amer* p. 313 March, 1947.

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CHAPTER XII

Food Requirement

Introduction. Every diabetic patient must give special attention to his diet for best results. The restrictions are not great. In fact, *uniformity of an adequate diet from day to day is the most important feature of the dietary therapy* for diabetes, rather than the severe restrictions as formerly practiced. The dietary needs will vary with the conditioning influences such as (a) change in occupation and physical activity, (b) obesity, indicating a reduced caloric intake but with a more liberal diet as the body weight approaches the desired level, and (c) acute complications during which a full quota of calories, protein and carbohydrate with an equally spaced distribution of the diet, throughout the twenty four hours permits better control of the diabetes with insulin.

In determining the diet, individualization in terms of so many grams of protein, carbohydrate and fat and the total calories, is the *first* requisite. The *second* is filling of the diet prescription in menu form. This menu will indicate certain food exchanges (see p 112), which permit a selection from a variety of foods without sacrificing uniformity of values. *Thirdly*, the patient is thoroughly trained in the use of household measures, viz, the teaspoon, tablespoon, ounce measure, cup, slice of bread, strip of bacon, etc., in accord with the food exchanges permitted in his specific diet.

This training we have found, is most effective if done by a dietitian who is especially qualified in simplifying the dietary program, in instructing the patient in the latitude of the selection of foods permitted and in accurately completing the menus. Weighing of the food is rarely necessary in the treatment for uncomplicated diabetes.

DIETARY NEEDS

A. Normal. Dietary needs are conditioned by age, sex, body weight and occupation. The *protein* intake for the normal adult ranges from 60 to 120 grams, the *fat*, 60 to 120 grams, *carbohydrate*, 250 to 400 grams, and *total calories* from 1780 to 3160.

B. Diabetic. The patient whose diabetes is well controlled needs no more and no less food to accomplish the same result than the normal per

son but there is greater urgency to restrict the calories for diabetic patients who are overweight and a modest reduction of the carbohydrate for nearly all diabetics simplifies the control of the diabetes.

Total Calories The total calories are a most important consideration in planning the diabetic diet. One of the fundamental principles in the dietary treatment of the diabetic patient is to avoid overfeeding and for the patients over thirty five years of age the body weight, barring certain

TABLE 13

THE BENEFICIAL EFFECT OF A DIET LOW IN CALORIES IN THE CASE OF AN OBESE DIABETIC PATIENT

(E. D. female 36 years of age Ht 66 inches Wt 211 pounds)

DATE	B	F	C	CAL.	BLOOD SUGAR (MG /100 CC.)	URINE SUGAR	INSULIN (UNITS)	WEIGHT (LB.)
1949								
March 10	110	90	200	2100		0-1+	100	211
11	100	33	100	1100	110	0	110	
12						0	110	
13						0-4+	110	
14				"		0	110	209
15						0	110	
16	"					0	110	
17					31	0	None	
18					143	0		
19						0		
20		"				0		
21	"	"	"			0	"	
22						0		

Subsequent tests following the patient's discharge from the hospital

April 1	100	111	100	1100	160	0	None	200
April 7					11"	0		199½
May 5					107	0		193
June 16					90	0		189
July 21					119	0	"	18"
Sept. 1			"	"	124	0		182

complications (p. 210) should be brought to 5 to 10 per cent below the standard weight (see Appendix p. 265) for his age, height and sex. Thus thin patients are fattened, obese patients are reduced, and patients of standard weight are subjected to a minor reduction in weight.

Changes in the total calories have a more far reaching effect on the insulin requirement than have changes in the allowance of carbohydrate (see p. 135).

Approximately 75 per cent of adult diabetic patients are overweight when they first seek medical attention because of their diabetes. All authori-

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In determining the diet, individualization, in terms of so many grams of protein, carbohydrate and fat and the total calories, is the *first* requisite. The *second* is filling of the diet prescription in menu form. This menu will indicate certain food exchanges (see p 112), which permit a selection from a variety of foods without sacrificing uniformity of values. *Thirdly*, the patient is thoroughly trained in the use of household measures, viz, the teaspoon, tablespoon, ounce measure, cup, slice of bread, strip of bacon, etc., in accord with the food exchanges permitted in his specific diet.

This training, we have found, is most effective if done by a dietitian who is especially qualified in simplifying the dietary program in instructing the patient in the latitude of the selection of foods permitted, and in accurately completing the menus. Weighing of the food is rarely necessary in the treatment for uncomplicated diabetes.

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1949								
March 10	110	90	200	2100		0-1+	150	211
11	100	33	100	2100	110	0	110	
12						0	110	
13						0-4+	110	
14						0	110	209
15						0	110	
16						0	110	
17					81	0	None	
18					143	0		
19						0		
20						0		
21						0		
22						0		

Subsequent tests following the patient's discharge from the hospital

April 1	100	111	100	1100	160	0	None	203
April 7					11"	0		199½
May 5					107	0		193
June 16					90	0		189
July 21					119	0		187
Sept 1					124	0		182

complications (p 210) should be brought to 5 to 10 per cent below the standard weight (see Appendix p 265) for his age height and sex. Thus thin patients are fattened obese patients are reduced and patients of standard weight are subjected to a minor reduction in weight.

Changes in the total calories have a more far reaching effect on the insulin requirement than have changes in the allowance of carbohydrate (see p 135).

Approximately 75 per cent of adult diabetic patients are overweight when they first seek medical attention because of their diabetes. All authors

ties on diabetes agree that the *obese diabetic patient* should be reduced, yet the neglect of this important method of controlling the disease and avoiding the use of insulin is widespread. The untreated obese diabetic patient has a mild diabetes and, barring complications, control of the disorder can be achieved and maintained by reducing the caloric intake sufficiently to bring about a slow reduction in weight—about two pounds per week. Data from the case records of two obese diabetic patients are presented in Tables 13 and 22 to illustrate the magnitude of the advantages of reducing the body weight. The great saving of insulin and the ease with which the diabetes is controlled are exemplified. All will agree that the reduction in weight, in itself, will greatly enhance the life expectancy. Patient, E D, although admitted in coma (March 4, 1949) with a blood sugar of 1450 mg per 100 cc, had an inherently mild diabetes, as shown by the ease with which it was eventually controlled by restricting the caloric intake and securing a reduction in body weight. The prompt elimination of such a large dose of insulin—110 units daily—would be a hazardous undertaking in the case of a thin patient but in the obese subject who is relatively resistant to insulin this can be done without fear in the absence of acute complications. For the overweight patient, a diet low in calories (see p 107) will achieve a proper reduction in weight. As soon as the diabetes is controlled, the rate of reduction may be cut in half by gradually increasing the caloric intake. When the body weight reaches a trifle below the standard level further increases in the diet are made to prevent continued loss of weight. Suitable adjustments are made in the early control phase and in the eventual long term treatment period to regulate the rate of reduction and to achieve a stationary weight at a desirable level.

By using the formula for prescribing the diet as outlined on page 106, it will be found that the individual with a *body weight closely approximating that of the normal* will have a more liberal diet than the overweight patient. One dose of insulin daily will probably be needed. The *underweight patient* will need a diet adequate to promote a gain in weight and because of the liberal diet and the increasing total body mass and total metabolism, insulin therapy will be essential.

Protein. We have been more liberal with protein in the past few years and have gained the impression that diabetic patients have a better sense of well being when the protein intake exceeds, by a small margin, that ordinarily consumed by a normal person. As a result, it is unusual to prescribe less than 100 grams of protein for the adult male and less than 90 grams for the adult female diabetic.

The diabetic's need for protein is the same as that of the nondiabetic as long as the diabetes is well controlled. A protein deficit occurs if large amounts of sugar are lost in the urine. To correct this feature a liberal allowance of protein, in excess of the normal allowance, and the control

of the diabetes are indicated. For the actual estimation of the protein quotas for the individual patient, see page 106.

Need for increased protein during growth and in the treatment for certain complications, notably hepatitis, pregnancy, cirrhosis of the liver and nephrosis, is recognized and appropriate amounts are prescribed.

Carbohydrate The carbohydrate allowance varies with the severity of the diabetes. In the case of the overweight patient with mild diabetes insulin therapy can be avoided by the continued restrictions of total calories and carbohydrate. These restrictions are relaxed as the body weight decreases and it is not unusual to find these patients tolerating eventually a diet of nearly normal content—carbohydrate, protein, fat and total calories, without hyperglycemia or glycosuria. *It is desirable to have the long term diet contain 225 to 300 grams of carbohydrate.*

For the underweight diabetic there is ordinarily no escape from insulin therapy and, as small increases in the insulin dosage permit large increases in carbohydrate, liberal quotas of carbohydrate are allowed at once—as much as 200 grams—with additions to 250 and infrequently to 300 grams after the diabetes is controlled.

Fat Fat is used to make up the calories not provided by the protein and carbohydrate. Each gram of protein and of carbohydrate can be considered as providing 4 calories, and each gram of fat 9 calories. Hence the calculation of the fat allowance is a simple matter. Because of the lipemia and the hypercholesterolemia so commonly associated with diabetes, and the effect of fat on the body weight we prefer to keep the fat content of the diet as low as is practicable. It is better to give higher carbohydrate quotas and control the diabetes with insulin when necessary, and to keep the fat content of the diet lower than has formerly been the practice. Fat in excess of 100 grams daily is rarely justified. It is highly probable that the degenerative changes in the vascular system will be less if the fat intake is kept down to 50 gm. daily as advocated by Rabinowitch.¹ A compromise—between 50 and 100 gm.—at this stage is justifiable. Such allowances will force the carbohydrate and protein quotas upward. This is permissible. Diets extremely low in fat—less than 40 gm. daily—are unpalatable, but with 50 to 75 gm. of fat there need be no sacrifice of palatability.

Distribution of Meals Uniformity of distribution of the diet from day to day reduces the amplitude of the oscillations in the blood sugar concentrations and permits better control of the diabetes than when no two successive breakfasts are alike or no two lunches or no two dinners. The diet is adjusted to the individual's needs and the distribution arrived at, as indicated below, is maintained from day to day until new circumstances warrant a change. The most common distributions of the diet as illustrated in Figures 17, 18 and 19, are

(a) For the patient having a mild diabetes and *not requiring insulin* the carbohydrate protein and fat are divided equally among the three meals. There is no objection to withholding a portion of any meal to be eaten between that mealtime and next, or some from each meal as illustrated in Figure 17, page 109, for a bedtime nourishment.

(b) For the patient taking a single dose of *protamine zinc insulin* the outline for three meals (Fig. 18) shows that they are equal but a portion of the breakfast, usually a glass of milk and three soda crackers—one milk and one bread exchange—is withheld and taken at bedtime. (See illustrative diets on pages 125 to 132.) This practice serves a double purpose. First, it means the carbohydrate intake for breakfast is reduced at a time when the action of the morning insulin is not well under way, and second the bedtime nourishment reduces the likelihood of hypoglycemic reactions in the early morning hours and permits, because of this, a larger dose of protamine zinc insulin to be given than could be used with safety otherwise.

(c) For the patient taking a single dose of *globin* or of *NPH insulin* the diet is divided into three equal meals but, as with protamine zinc insulin, milk and crackers—one milk and one bread exchange—are withheld from breakfast, but in the case of globin insulin (Fig. 19) they are taken between 3 and 4 P. M. In this manner the likelihood of hypoglycemic reactions before supper is guarded against and larger amounts of globin insulin can be given without risk of hypoglycemia than could otherwise be done if this precaution were not taken. This is of great practical value since the larger the dose of globin insulin given the more quickly it acts and the longer the blood sugar lowering effect persists. Under these circumstances the results obtained with globin insulin more closely duplicate the results obtained with combined regular and protamine zinc insulin therapies.

(d) For the patient taking a dose each of *protamine zinc* and *regular insulin*, separately or mixed with or without a small pre supper dose of regular insulin, as is necessary in some severe and labile cases, the diet is divided into three equal meals. No food is withheld from breakfast because in this case the protamine zinc insulin is being supplemented by the rapidly acting regular insulin. It is permissible if the patient wishes, to eat a small portion of the lunch at 11 A. M. This practice reduces the chances of a hypoglycemia—due to the regular insulin—just before lunch. Also the same need to prevent a hypoglycemia in the early morning exists as in (b) above and to accomplish this a glass of milk and two graham crackers—one milk and one bread exchange—are taken from the evening meal (Fig. 19) or given, in addition to the prescribed diet at bedtime.

The distribution of the diet in the presence of acute complications is considered on pages 217 to 221.

Influence of Complications During acute complications particularly infections, which greatly alter the effectiveness of insulin it has been

our practice since 1932 to divide the diet into four equal meals, one given every six hours, or in very rare instances where several hundreds of units of insulin are given in each twenty four hours, the diet is divided into six equal meals and one is given in liquid or soft form, every four hours. This feature is dealt with in more detail on pages 217 to 221.

This plan of therapy during acute complications has received wide spread adoption. It permits the control of the diabetes no matter how severe it may be. The control one secures over the diabetes by this measure during acute complications is comparable to the secure control over an automobile which follows when one shifts from high to low gear.

Surgical complications, like infections, temporarily increase the severity of the diabetes, and make the administration of insulin necessary. This is true even if the diabetes is mild and insulin is not ordinarily needed. The diabetic patient who is undergoing a surgical operation, like the patient with an infection, needs a feeding every six hours, each preceded by a dose of regular insulin. The details of the management of these patients will be considered in Chapter XVI.

The presence of arterial hypertension or of congestive heart failure in a diabetic patient necessitates restriction in the salt intake in addition to the diabetic diet, and the presence of hypercholesterolemia or of xanthoma diabetorum necessitates restriction of fat and a more liberal use of carbohydrate than is ordinarily indicated.

Standardized Diets. Convenience is served in the use of standardized diets and for most patients with uncomplicated diabetes, such diets are satisfactory. Eleven standard diets are presented in Table 18 and on pages 122 to 132. The diet most closely approximating in total calories, the diet prescription discussed in Chapter XIII is adopted for the individual patient and suitable changes to the more liberal or the more restricted diets are made if indicated by alterations in body weight.

Standardized diets are not applicable in dealing with acute complications, such as nephritis with nitrogen retention and duodenal ulcers. Diets for such patients must be more highly individualized and made to conform with the diet which experience has shown to be most effective in treatment for existing complications. Uniformity of the diet from day to day will permit adequate control of the diabetes, a factor which is usually of no small importance in fortifying the therapy for the complicating disorder.

The use of standard diets for patients thoroughly instructed in the flexibilities made possible by using the various food exchanges has simplified greatly the dietetic aspects of the therapy for diabetes.

The foregoing plan of dietetic treatment adheres in principle to that advised by Allen and by Joslin though we are more liberal with the protein and carbohydrate quotas but rely greatly on restricted fat and total calories in treating diabetic patients who are overweight.

The more liberal protein allowance adds remarkably to the 'staying value' of a meal. Also, the appetite is more effectively satisfied. Because of these advantages that are apparent, and others not so apparent, it is unusual that the so called permanent or long term diet of the adult contains less than 90 grams of protein. The carbohydrate allowance is higher than recommended by Joslin and his associates. We favor this increase because it permits a lower fat intake and because it has been proven by Allen and observed many times by us that great increases in carbohydrate are permissible with but little change in the need for insulin, provided the total calories are not increased at the same time—appropriate reductions being made in the fat intake. Also, the high incidences of lipemia and hypercholesterolemia and the tendency to degenerative changes in the vascular system in diabetics encourage us to increase the carbohydrate and to decrease the fat to the limits of practicability.

Contrast with Other Diets Diets of historical interest are commented upon in the Chapter on History. The diets of today vary greatly. We believe the diet prescriptions presented in this book are those which, in general, are used most widely. We tend to give more liberal allowances of carbohydrate and protein than many but somewhat less carbohydrate than is included in "Free Diets."

In general, three types of diet are considered in present day medical writings:

1 The more conservative diet with liberal protein, nearly normal carbohydrate and with the total calories regulated according to the dictates of the body weight. This measured diet is aimed, with suitable use of insulin, at restoring physiologic processes, as closely as is practicable, to normal. We think of this plan of therapy as the *Physiologic Plan*.

2 The high carbohydrate, low fat and low calorie diet advocated by Rabinowitch¹ is standing the test of time and has much in its favor. An illustrative diet is as follows: Protein, 70 grams, Carbohydrate, 400 grams, and Fat, 50 grams (2330 calories).

3 Free diets as recommended by Stolte² are advocated by Tolstoi.³ These are normal diets, not weighed or measured. Insulin is used to prevent symptoms but otherwise glycosuria and hyperglycemia are disregarded. We believe that this program fosters the maintenance of an unphysiologic state and one which, by permitting hyperglycemia over long periods, predisposes to early degenerative changes. Diabetic neuropathies, increased susceptibility to tuberculosis and increased hazards during pregnancy are characteristically more prevalent in patients with uncontrolled diabetes. It appears inescapable, from accumulating clinical data, that a penalty will eventually be exacted—a penalty which otherwise might be prevented in some, and postponed in others.

Vitamins and Minerals *Vitamins* There is no convincing evidence that vitamin therapy has a more specific benefit for the diabetic patient

TABLE 13
RECOMMENDED DAILY DIETARY ALLOWANCES*
REVISED 1918

Food and Nutrition Board National Research Council Washington D. C.

	CALORIES	PROTEIN	CAL- CIUM	IRON	VITA- MIN A ²	THIA- MIN ³	RIBO- FLA- VIN ²	NIACIN (NICO- TINIC ACID) ¹	AS- CORBIC ACID	VITA- MIN D
		grams	grams	mg	I U	mg	mg	mg	mg	I U
Man (154 lb 70 kg)										
Sedentary	2400	70	10	12 ⁴	5000	1.2	1.8	12	75	1
Physically ac- tive	3000	70	10	12 ⁴	5000	1.5	1.8	15	75	1
With heavy work	4500	70	10	12 ⁴	5000	1.8	1.8	18	75	1
Woman (123 lb 56 kg)										
Sedentary	2000	60	10	12	5000	1.0	1.5	10	70	
Moderately ac- tive	2500	60	10	12	5000	1.2	1.5	12	70	1
Very active	3000	60	10	12	5000	1.5	1.5	15	70	1
Pregnancy (lat- ter half)	2400 ⁵	80	15	15	6000	1.5	2.5	15	100	400
Lactation	3000	100	20	15	8000	1.5	3.0	15	150	400
Children up to 12 yrs ¹										
Under 1 yr ⁶	110/2 2 lb (1 kg)	5 5/2 2 lb (1 kg)	10	6	1500	0.4	0.6	4	30	400
1-3 yrs (27 lb 12 kg)	1400	40	10	7	2000	0.6	0.9	6	35	400
4-6 yrs (42 lb 19 kg)	1600	50	10	8	2500	0.8	1.2	8	50	400
7-9 yrs (58 lb 26 kg)	2000	60	10	10	3500	1.0	1.5	10	60	400
10-12 yrs (78 lb 35 kg)	2500	70	12	12	4000	1.2	1.8	12	75	400
Children over 12 yrs ¹										
Girls 13-15 yrs (108 lb 49 kg)	2600	80	15	15	5000	1.3	2.0	13	80	400
16-20 yrs (122 lb 55 kg)	2400	75	10	15	5000	1.2	1.8	12	80	400
Boys 13-15 yrs (108 lb 49 kg)	3000	85	15	15	5000	1.5	2.0	15	90	400
16-20 yrs (141 lb 64 kg)	3800	100	15	15	6000	1.7	2.5	17	100	400

Vitamin A

¹ For adults (except pregnant and lactating women) receiving diets supplying 2000 calories or less.
² The range of the unit is 1000 to 10000 IU respectively.

⁴ There is evidence that the male adult needs relatively little iron. The need is about 10 mg per day.

diet for uncomplicated diabetes. The loss of sodium chloride in polyuria may create a craving for salt in the untreated diabetic. Also, as ketosis appears and progresses unfavorably, the loss of sodium chloride may reach grave proportions. Sodium chloride administered early in the treatment of ketosis is an effective supplementary measure in preventing peripheral vascular collapse (see p. 230).

Calcium and potassium also are present in adequate amounts in the usual diet for the uncomplicated diabetic. Great losses of both of these minerals occur in ketosis. Decalcification of the bones is common in the elderly diabetic. The inclusion of a pint of whole milk or skimmed milk in the daily diet for the adult and a quart of whole milk for the child will prevent calcium and potassium depletion in the absence of complications. Special consideration is given to the potassium intake in ketotic patients (see p. 238) in whom a hypokalaemia may be a cause of death.

Iron Deficiency. The absorption of iron is interfered with in cases of achlorhydria—a common occurrence in diabetes in patients past forty five

above the preceding level. The value of 2100 caloric units represents the allowance for pregnant, sedentary women.

Allowances for children are based on the needs for the middle year of each group (see 2, 5, 8, etc.) and are for good rate of activity and for average weight at the middle year of the age group.

Needs for infants increase from month to month with size and activity. The amounts given are for approximately 6 to 8 months. The dietary requirements for some of the nutrients such as protein and caloric units are less if derived largely from human milk.

Further recommendations:

Fat. There is available little information concerning the human requirement for fat. Fat allowances must be based at present more on food habits than on physiological requirements. While a requirement for certain unsaturated fatty acids (the linoleic and arachidonic acids of animal fats) has been amply demonstrated in the experimental animals, the human need for these same fatty acids is not known. In spite of the paucity of information on this subject, there are several factors which make it desirable (1) that fat be included in the diet to the extent of at least 20 to 25 per cent of the total calories and (2) that the fat intake include a certain amount of unsaturated fatty acids to the extent of at least 1 per cent of the total calories. At higher levels of caloric expenditure, e.g., for a very active person consuming 4000 calories and 150 g. of fat, and for adolescent persons, it is desirable that 30 to 35 per cent of the total calories be derived from fat. Some foodstuffs such as meat, milk, cheese, nuts, etc., contribute fat to the diet, it is unnecessary to use separated or vegetable fats such as butter, oleomargarine, lard, or shortenings only to supply one-third to one-half the amount indicated.

Water. A usual allowance of water for adults is 2.5 to 3 liters daily in most climates. An ordinary standard for a very person is one or 1.5 liter for each calorie of food. Most of this is contained in a prepared food. At work or in hot weather, requirements may reach 5 to 10 liters daily. Water should be allowed ad libitum, and sensations of thirst usually serve as adequate guides to intake except for infants and sick persons.

Salt. The needs for salt and for water are closely interrelated. A liberal allowance of sodium chloride for the adult is 5 grams daily except for some persons who sweat profusely. The average normal intake of salt is 10 to 15 grams daily, an amount which meets the salt requirements for a water intake up to 4 liters daily. When sweating is excessive, one additional gram of salt should be consumed for each liter of water in excess of 4 liters daily. With heavy work or in hot climates, 10 to 30 grams daily may be consumed with meals and in drinking water. Even three most persons do not need more salt than usually occurs in prepared foods. It has been shown that after salt metabolism on persons produce sweat that contains only about 0.5 gram to the liter in contrast with a content of 2 to 3 gram for sweat of the uncompensated person. Consequently after salt metabolism need for increase of salt beyond that of ordinary food is apparent.

Iron. The requirement for iron is small, probably about 0.002 to 0.004 mg. daily for each kilo gram of body weight, or a total of 0.15 to 0.30 mg. daily for the adult. This need is met by the regular use of red meat, salt is also especially important in adolescence and pregnancy.

Phosphorus. Available evidence indicates that the phosphorus allowance should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation. In the case of other adults the phosphorus allowance should be approximately 1.5 times that for calcium. In general it is safe to assume that if the calcium and protein needs are met through common foods, the phosphorus requirement also will be covered, because the common foods richest in calcium and protein are also the best sources of phosphorus.

Copper. The requirement for copper for adults is about 1 to 2 mg. daily. Infants and children require approximately 0.05 mg. for each kilogram of body weight. The requirement for copper is approximately one-eighth that for iron. A good diet normally will supply sufficient copper.

Vitamin A. The requirement for vitamin A is usually not met by any good diet except for the infant, a vitamin and for the first few days after birth. In experimental vitamin A deficiency is recommended during the last month of pregnancy. When it has not been given during the pregnancy, it is recommended for the mother preceding delivery or for the baby.

Vitamin B. Evidence for some vitamin B is an essential nutrient and vitamin B₁₂ is a case factor or quantitative requirement cannot be clearly established from

SINGH

years of age Iron therapy in such cases should be in conjunction with the administration of dilute hydrochloric acid The prescription of $\frac{1}{2}$ dram each of dilute hydrochloric acid and essence of pepsin in a glass of water with each meal plus iron therapy is recommended * Iron depletion associated with achlorhydria in the female during her reproductive years is exceptionally amenable to this combined therapy

Ferrous sulfate 0.2 to 0.3 gm (3 to 5 grains), given orally, three times daily after meals, is effective in many cases of hypochromic anemia without achlorhydria

Choline, or a combination of choline, methionine and inositol (methischol) is administered three or four times daily in cases in which there is enlargement of the liver due to deposits of fat

* For patients who prefer tablets or capsules to liquid medicines, Glutamic acid hydrochloride (Lilly) is available in pulvules for administration with ferrous sulfate Each pulvule of this preparation dispensed as "Acidulin" is equivalent to 10 m mms of dilute hydrochloric acid U.S.P.

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CHAPTER XIII

Treatment

INTRODUCTION AND DIET

Introduction. The treatment of the diabetic patient embraces the control of the physiologic disturbances, in so far as this is practicable, and the guiding and reassuring of the patient in the readjustments which are inevitable with the onset or disclosure of a chronic and, to all intents and purposes, an incurable disease which still carries, to the uninformed, grim stigmata of the past. Reassurance and instruction, especially concerning the diabetes, are important until the patient understands that he will not be starved, that he will be relieved of his symptoms, that he can anticipate a nearly normal life expectancy, that he, himself, will be the helmsman in conducting the treatment—a most reassuring feature when he is qualified to be his own helmsman—and that he will not need to change his occupation, except in rare instances, or give up customary activities.

In short, diabetes, though it is a chronic disease is controllable and the changes for the patient will be the improved health he will enjoy when treatment gets under way, the adoption of a more uniform plan of eating and exercising from day to day, and the administration of insulin if necessary.

Reassurance, in the early days of his diabetes when he is apt to be needlessly concerned, is an important phase of the preparation of the patient for a lifetime plan of treatment. The psychologic aspect and the physiologic therapy are inseparable and both should be conducted by the internist rather than dividing responsibilities with a psychiatrist.

The treatment for diabetes is not a simple one and, while a certain degree of uniformity exists in the measures employed, no two patients will be treated in identically the same manner. The *objectives* are to provide relief from symptoms, to restore as nearly as is practicable, a normal physiologic state with freedom from hyperglycemia, glycosuria, hyperlipemia and hypercholesterolemia, to promote normal development physically and mentally, to restore and maintain a high standard of nutrition that will stabilize the body weight at a desirable level, to prevent complications and to reduce the risks to which patients with diabetes are exposed,

e.g., infections, surgery, pregnancy and accidents, and to have these patients partake of varied activities which will culminate in an enjoyment of a full life. A due regard for the patient as a whole, and not only for his blood sugar level and glycosuria, is important for overall good results.

Blood sugar values restored to and maintained within the normal range of fluctuation can have none other than a good result when wisely done. It is true that in some cases too strenuous efforts to maintain a normal blood sugar may increase the risk of hypoglycemic reactions. However, the proper distribution of the diet and the correct selection and combination of insulins, and the exercise of good clinical judgment comprise the methods of solving these problems. The glycosuria will subside with proper treatment in most cases and the immediate symptoms of diabetes will be abruptly stopped. Certain cases of a peculiarly labile diabetes present special difficulties (see p. 256).

The means available for correcting the physiologic disturbances associated with diabetes are (a) dietary management, (b) insulin, (c) training of the patient, (d) exercise, (e) general care, and (f) miscellaneous measures.

Treatment is most effective if the initial phase is carried out in a hospital with the patient on an ambulatory basis. A few days—usually four or five—suffice to gain an acquaintance with the characteristics of the individual, to have treatment instituted under controlled conditions, to evaluate the diabetes and decide on the measures most suited for the individual, to observe the initial response to these measures and—of greatest importance—to train the patient in diet management, insulin therapy, testing the urine, and special hygiene.

The initial treatment or so called "standardization" conducted at the physician's office is time consuming and is often doomed to failure. In the unusual instance, however, and where a properly trained office personnel is available, the efforts may be rewarded with success. We know of nothing, however, that has such a lasting impression on these patients as the hospital routine and training, and we know of no patient who regretted having had this experience.

Diet. Every diabetic patient should be diet-conscious. He should be aware of the degree of flexibility of the diet permitted in his case and he should understand why there should be quantitative uniformity in diet and regularity of meal time from day to day. The objectives of the diet therapy for diabetics are: adequate *calories* to restore and maintain a near normal body weight, a normal or slightly higher than normal *protein* intake with slight restriction in the *carbohydrate* with sufficient *fat* to provide the calories not provided by the protein and carbohydrate. There should be no short changing in minerals nor vitamins and finally, when the optimum diet distribution is decided upon, this plan should be adhered to from day to day. To eat a large breakfast and small lunch one day and

the reverse on the next would create undesirable fluctuations of the blood sugar

Prescription of the Diet for the Diabetic Patient Having No Acute Complication The initial diet is, at best, a trial diet and alterations are necessary, in most cases, as circumstances change. The dietary requirements will vary with sex, age, growth, body build and weight, activities, response to treatment, the severity of the diabetes—and whether the patient needs insulin or not—and complications. It is clear that there is no permanently fixed diet for the individual but one which is subject to changes as one or a combination of circumstances dictate. However, the aim is to arrive at the diet which will meet all essential requirements and be relatively uniform from day to day. In accomplishing this end the following major features are taken into account:

- (a) Total calories
- (b) Protein
- (c) Carbohydrate
- (d) Fat
- (e) Minerals and vitamins (See pp. 98 and 99)

In general, overfeeding is avoided, a little more protein than formerly prescribed is permitted, the carbohydrate allowance is increased to quotas closely comparable with those of normal diets, and the fat is kept as low as is practicable—below 100 grams in the great majority of cases. We share, to a considerable degree, Rabinowitch's respect for a low fat and a more liberal quota of carbohydrate.

TOTAL CALORIES The total caloric value of the diet is one of the most important considerations when dealing with the dietary needs of the diabetic patient and changes in the total caloric content of the diet have a far reaching effect in the control of the diabetes. These features are emphasized especially in the treatment of the overweight patients who comprise over 70 per cent of the new diabetic patients seen month after month by general practitioners. This is a fact that might easily be overlooked when it is realized that most medical writings on the subject of diabetes deal with patients who need insulin. The most satisfactorily effective manner of controlling the diabetes in overweight patients is to reduce their weight by means of a reduced caloric intake. All authorities are agreed that the obese diabetic should be reduced in weight and yet it is incomprehensible why this efficient means of controlling the disease, and avoiding the use of insulin, is so often entirely neglected. The untreated obese diabetic patient has a mild diabetes despite the degree of hyperglycemia and, barring acute complications, control of the diabetes can be maintained readily by reducing the caloric intake sufficiently to accomplish a slow reduction in weight.

The American Diabetes Association through its Educational Commit

tee, is fostering a uniform method of prescribing diets for diabetic patients. With certain modifications, the following plan conforms with their recommendations, except that here we employ measures to reduce the obese patient more rapidly and we allow more protein and more carbohydrate in the diets and hence, less fat.

Total Calories (a) To estimate the approximate basic caloric requirement for twenty four hours, multiply the ideal body weight (see Appendix) in pounds* by 10. Add 100 to 200 calories if the patient is a young tall male, deduct 100 to 200 calories if the patient is elderly, short, or female, or if the patient is obese deduct 200 to 400 calories. (b) For a patient with ordinary light activities the diet should usually provide 30 per cent more than the basal calories and, with greater activity, 50 to 75 per cent more than the basal calories (see illustrative diets, p. 107).

Example Female patient fifty five years of age, ideal weight 140 pounds, light activity

Multiply ideal weight by 10 (140 x 10)	1400 calories
Correction for age and sex, deduct	100 calories
Basal calories	1300 calories
Add 30 per cent	390 calories
Maintenance diet (Total)	1690 calories

PROTEIN Multiply the ideal weight in pounds by $\frac{7}{16}$ to determine the protein in grams—children will need higher quotas of protein (Chap. XIX).

CARBOHYDRATE The carbohydrate allowance is influenced by the total calories permitted and the severity of the diabetes and, in particular, by whether or not insulin therapy is needed. Accordingly, the plan of prescribing this dietary component is as follows:

(a) *Carbohydrate allowance—100 to 125 grams—for the obese diabetic receiving a low caloric intake and no insulin.* As the diabetes is controlled and the body weight reduced additions are made at relatively long intervals until the diet contains 250 to 300 grams of carbohydrate.

(b) *Carbohydrate allowance—250 grams—for the patient who is underweight or normal weight and who needs insulin.* Increases to 275 and occasionally to 300 grams are desirable if such a liberal quota does not appreciably increase the difficulty in controlling the diabetes.

FAT The balance of the calories not provided by protein and carbohydrate are made up with fat, e.g., a diet containing 100 gm. protein, 275 gm. carbohydrate and 2200 calories will need 77 gm. of fat viz.,

* Pounds are used in preference to kilograms. This is done without sacrifice of any benefit and because scales for weighing purposes on this continent record weights in pounds and because the computation of kilograms from pounds is avoided.

Protein	100 gm.	400 calories
Carbohydrate	275 gm	1100 calories
	Total	1500 calories
Balance of calories to be made up with fat		
$2200 - 1500 = 700$ calories $700 \div 9 = 77$ gm. of fat.		

The prescription of the diet may be simplified by merely deciding upon the total calories and adopting the standard diet outlined in Table 18, in which the total calories most nearly approximate that of the prescribed diet

Illustrative Diet Prescriptions For A Obese diabetic patient, female, aged fifty five years, actual weight 180 pounds, ideal weight 136 pounds, light activity.

Multiply ideal weight by 10 (136×10)	1360 calories
Correction for age, sex, degree of obesity, deduct	400 calories
	960 calories
Add 30 per cent for light activity	288 calories
Total	1248 calories

As diet No III (p 124) approximates this total caloric value it may be selected without further calculation. It will be found to check closely. However, the diet prescription may be carried on to include protein and carbohydrate, viz

Protein	$\frac{1}{2} \times 136$	85 gm
Carbohydrate		130 gm.
Fat = $1248 - 860 = 388$ calories $388 \div 9 = 43$ gm		

D Patient of normal weight, male, age thirty two, actual weight 150 pounds, ideal weight 150 pounds, light activity and receives insulin

Multiply ideal weight by 10 (150×10)	1500 calories
Correction for age and sex, add	200 calories
	1700 calories
Add 30 per cent for light activity	510 calories
Total	2210 calories

The total calories, as calculated, most closely approach that of Diet No VIII (p 129) hence this diet can be prescribed without further calculation. Or, if the entire diet prescription is computed it would be as follows:

Protein	$\frac{1}{2} \times 150$	93 gm.
Carbohydrate (250 to 275 gm)		275 gm.
Fat = $2210 - 1472 = 738$ calories $738 \div 9 = 82$ gm		

This difference between the diet calculated in this manner, and diet No VIII, or diet No VII is not sufficient to be of great clinical significance.

C Underweight diabetic patient, female, age eighteen, actual weight 96 pounds, ideal weight 132 pounds, quite active and receives insulin

Multiply ideal weight by 10 (132×10)	1320 calories
Correction for age and sex deduct	100 calories
	1220 calories
Correction for activity 75 per cent add	915 calories
Total	2135 calories

The total calories as estimated most closely approximate those of diet No VII (p 128) This diet may be employed without additional calculation. However, individual calculation of the other dietary components would indicate

Protein	$\frac{6}{8} \times 132$	80 gm
Carbohydrate		260 gm
Fat = $2135 - 1360 = 775$ calories	$775 \div 9 = 86$	gm.

Adjustments in the diets are made at infrequent intervals after the initial stages of therapy

In the case of the obese patient the rate of the reduction of body weight may be slowed up to a pound or two per month as soon as the diabetes is controlled. Suitable increases in the total caloric allowance of the diet are made to secure this end. When the body weight reaches the standard level which may require several months, further increases are made to prevent little if any further decreases in weight. The return to an obese state, of course, would restore the hazards which accompany it. Patients are warned of this.

Diets of a low caloric value are employed to reduce weight and to secure the benefits that follow but care should be taken that they do no harm. It is especially important that the intake of certain vital food factors should not be reduced beyond the minimal requirements. In fact, as indicated on page 99, the diabetic patient may need more of the vitamin B complex than do normal individuals.

Distribution of Meals in Relation to Insulin Therapy Appropriate distribution of meals permits better control of the diabetes and decreases remarkably the risk of hypoglycemic reactions. The accomplishment of these desirable features and the allowance of an adequate diet with great flexibility in the choice of foods comprise our chief reason for adhering to a form of therapy that comes close to physiologic control of the diabetes. This is in preference to measures which permit what we consider to be unwarranted degrees of hyperglycemia and glycosuria.

On first thought these dietary considerations may appear confusing but they are based on well founded principles and have proved to be most satisfactory. Other combinations than those presented may prove to be equally effective but for the sake of simplicity only the programs we have found to be most satisfactory with the respective insulin treatments are presented. It will be observed that when the ideal program of insulin therapy (more fully discussed in Chapter XIV) is determined the distribution of the diet becomes automatic. In this manner decreases are made in meals preceding

the period in which a hyperglycemia is likely and more liberal food intake is permitted preceding periods in which hypoglycemia reactions might otherwise occur

A No insulin For the diabetic receiving no insulin a portion is taken from the total diet for a bedtime nourishment. In the case of very low caloric diets, e.g. diet No. 1 (900 calories), this nourishment must necessarily be scant. In fact, a glass of skim milk—one milk exchange with the fat omitted—is all that is allowed on the diet referred to. But when 1100 calories are permitted, a bedtime nourishment of 1 graham cracker— $\frac{1}{2}$ of a bread exchange—is added as indicated in diet No. 11, page 123.

The diet values, after the bedtime nourishment is deducted, are divided into three equal meals—for breakfast, lunch and supper, as indicated in



Fig. 17 Depicts the deduction of a nourishment from the total diet for a bedtime nourishment. This method of dividing the diet is employed.

A When no insulin is needed (see diets I, II, III and IV on pages 122 to 126)

B When a combination of regular and protamine zinc insulin—separately or mixed—is given before breakfast with a dose of regular insulin before supper

Figure 17 The deduction of food from the main meals serves to decrease the peaks of demand for insulin and the evening nourishment aids in correcting and in preventing excessive hunger, a favorable feature when the diets are small, as is frequently the case when insulin is not needed.*

B. One dose of protamine zinc insulin daily before breakfast In this instance a portion of the breakfast—one milk and one bread exchange—is deducted and given at bedtime (Fig. 18). The small breakfast is advantageous because of the slowness of the protamine zinc insulin in getting under way and the bedtime nourishment serves to reduce the likelihood of a hypoglycemia during the night when there is still considerable insulin activity.

C. One dose of globin insulin daily before breakfast is the indication for a portion—one milk and one carbohydrate exchange—of the breakfast for consumption between 3 and 4 P.M. (Fig. 18). The action of globin insulin is slow on the "take off," making a small breakfast desirable, and the greatest apparent insulin action being between 3 P.M. and supper time, a nourishment between 3 and 4 P.M. reduces or eliminates the likelihood of hyperglycemic reactions before supper.

D. One dose each of protamine zinc insulin and globin insulin daily

* Except when the caloric value of the diet is very low, as in diets No. 1 and No. 11, the usual values for bedtime nourishments are one milk and one bread exchange, e.g., one glass of milk and five saltine crackers.

before breakfast calls for a small breakfast with a nourishment between 3 and 4 P M, as a safeguard against a reaction due to globin insulin, and a bedtime nourishment to reduce the risk of a reaction due to protamine zinc insulin during the night and in the early morning. One nourishment—one milk and one carbohydrate exchange—is taken from the breakfast and the other, of equal value, is taken from the evening meal as indicated in Figure 19.

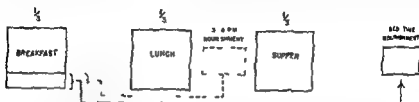


Fig 18 Illustrates diagrammatically the withdrawal of a nourishment from the breakfast menu for a bedtime snack when protamine zinc insulin only is taken before breakfast. The distribution when globin insulin is used is indicated by the broken line.

E One dose of protamine zinc insulin and one dose of regular insulin administered separately or as a mixture is balanced most satisfactorily with a liberal breakfast—one third of the total diet—a liberal lunch also one-third, and an evening meal from which a nourishment is deducted for consumption at bedtime as indicated in Figure 19.

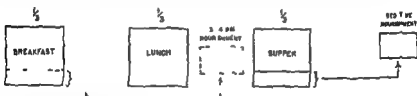


Fig 19 Illustrates diagrammatically the division of the diet.

A Solid lines—when regular insulin and protamine zinc insulin are given before breakfast.

B If a dose each of the deduction of a P M—indicated by

1/3 — breakfast and 4/3 — ment

solid and broken lines is also or when regular insulin is given

The rapid action of regular insulin is the reason for the liberal breakfast. The full third of the diet for lunch is advisable as the action of the regular insulin superimposed upon that of the protamine zinc insulin is still quite active well into the afternoon. This action has subsided by supper time hence the bedtime nourishment—one milk and one carbohydrate exchange—is taken from the evening meal. As in the foregoing instances the bedtime nourishment serves to neutralize the hypoglycemic effect of protamine zinc insulin between midnight and breakfast time.

F One dose each of regular insulin and protamine zinc insulin before breakfast, separately or mixed, and one injection of regular insulin before the evening meal This program, for patients having severe diabetes, indicates, according to principles already dealt with, a liberal breakfast, a liberal lunch, a liberal supper and a bedtime nourishment. Hence, as in 'A' (p 109), the bedtime nourishment—a milk and a carbohydrate exchange—is taken from the total diet before it is divided into the three main meals (Fig 17)

G One dose of NPH insulin The diet, in the case of a patient taking one dose of NPH insulin daily before breakfast, is divided in a manner that provides a small breakfast, a nourishment between 3 and 4 P M, and a bedtime nourishment as depicted in Figure 19. This distribution is used because of the slowness of the initial action of NPH insulin with the tendency to hyperglycemic values in the mid forenoon unless the breakfast is reduced. Some patients tend to have hypoglycemic reactions before supper, hence the 3 to 4 P M nourishment, but others are more prone to reactions during the night and it is for this reason that a bedtime nourishment is prescribed. This nourishment is deducted from the evening meal. It is well known that if the supper is divided in this manner the influence against a hypoglycemic reaction is much greater than if the same total food were all taken at one meal.

H One dose of NPH insulin to which regular insulin has been added This has been a very satisfactory mixture of insulins. We employ NPH with regular insulin in a proportion of 4:1 almost exclusively and with this mixture the same distribution of the diet as outlined in 'C' and indicated in Figure 19 is used, i e., a portion of breakfast is given between 3 and 4 P M and a portion of the supper at bedtime. It is true that, with the rapidly acting regular insulin added, the hyperglycemic tendency during the forenoon is eliminated and accordingly the breakfast need not be reduced. However, it simplifies matters to take the mid afternoon nourishment from the breakfast when the bedtime nourishment is taken from the supper. The risk of hypoglycemic reactions before lunch, because of the reduced breakfast, has not been a problem.

SIMPLIFIED METHOD OF COMPLETING THE MENU FROM A PRESCRIBED DIET—FOR THE PATIENT

The essentials in transposing the information contained in a diet prescription to a menu with the amount of each food for each meal are

1 A prescription for a diet, e g., protein 90 gm., carbohydrate 210 gm., and fat 55 gm. (1700 calories)

2 A familiarity with household measuring devices. You will need a standard 8 ounce measuring cup, a teaspoon and tablespoon. Level and not heaped measures are referred to in these pages.

3 Special information about foods

a Diets for diabetics are such that no special "diabetic foods"

necessary—the same foods used for the family are best Use in appropriate amounts milk, vegetables, meats, fats and fruits without added sugar (Indeed, some of the diets high in carbohydrate may contain sugar but this is an individual consideration and one to be settled by the physician in charge)

b Seasoning of foods is the same as for the nondiabetic when the following agents are used chopped parsley, mint, garlic, onion, celery, salt, nutmeg, mustard, cinnamon, pepper and other spices, lemon, saccharine and vinegar

c You may use freely, and without reducing your "diet account," coffee, tea, clear broth, bouillon (without fat), gelatin (unsweetened), rennet tablets, pickles (sour, or unsweetened dill), cranberries and rhubarb

4 A working knowledge of the source of food components *Carbohydrate* foods are fruits, cereals, breads, vegetables, etc *Protein* foods are meat, eggs, milk, nuts, etc *Fat* foods are butter, cream, margarine and olive oil

These food components may overlap For instance, while milk is considered a protein food it also contains fat and carbohydrate Also, bread and cereals are carbohydrate foods but contain some protein This overlapping has complicated diet problems in the past but with the adoption of the Exchange System it is now a simple matter to make an appropriate menu from a prescribed diet

5 A familiarity with the Exchange System* which is summarized in Table 15

TABLE 15
COMPOSITION OF FOOD EXCHANGES*

LIST	FOOD	MEASURES	GM	C	P	F	CAL
1	Milk Exchanges	$\frac{1}{2}$ pint	210	12	8	10	170
2a	Vegetable Exchanges	as desired					
2b	Vegetable Exchanges	$\frac{1}{2}$ cup	100	7	2		36
3	Fruit Exchanges	varies		10			40
4	Bread Exchanges	varies		15	2		80
5	Meat Exchanges	1 oz	30		7	5	73
6	Fat Exchanges	1 tsp	5			1	45

* Meal planning has been simplified by the introduction of the "Exchange System" which is summarized in Table 15.

MILK EXCHANGES—LIST 1

One exchange of milk contains 12 grams fat + 12 grams protein + 12 grams carbohydrate

Milk is one
plan to drink 1

This list shows

Type of Milk	Gm	Amount to Use
Whole milk (plain or homogenized)	210	1 cup
* Skim milk	210	1 cup
Evaporated milk	190	1 1/2 cup
Condensed milk		

VEGETABLE EXCHANGES—LIST 2

All vegetables contain sugar but some have more sugar than others. The vegetables have been divided into three groups according to the amount of sugar they have.

List 2 shows

VEGETABLE EXCHANGES A

(Contain little Carbohydrate Protein or Calorie)

You may use

* Broccoli	* Leafy Greens	* Okra
Brussels Sprouts	Chard	* Pepper
Cabbage	Collard	Radishes
Cauliflower	Dandelion	Sauerkraut
Celery	Kale	String Beans young
* Chicory	Mustard	Summer Squash
Cucumbers	Spinach	* Tomatoes
* Escarole	Turnip Greens	* Watercress
Eggplant	Lettuce	

* These vegetables contain significant amounts of vitamin A

VEGETABLE EXCHANGES B

(Contain more Carbohydrate Protein or Calorie)

These vegetables
use these vegetables
cooked vegetable
vegetable

* Beets	Pumpkin
* Carrots	Rutabagas
Onions	* Squash winter
Peas green	Turnip

* These vegetables are rich in vitamin A

You may serve vegetables plain or with part of the meat or fat exchange for seasoning. You may wish to use the vegetables, milk and meat exchanges in your meal plan together. In this way you can make soups, stews or other dishes.

For salads you may use mayonnaise or French dressing as your fat exchange. (For example if you use 1 teaspoon of mayonnaise you would give up 1 teaspoon of butter.) Zero salad dressing (recipe page 118) may be used as desired.

FRUIT EXCHANGES—LIST 3

One exchange of fruit contains 10 grams Carbohydrate and 40 Calories.

Each exchange of fruit shown below contains about the same amount of sugar. Your meal plan will tell you how many exchanges you can have each day. You may use your fruit fresh, dried, cooked, canned or frozen as long as no sugar has been added. Look at the label on the can or package to be sure it indicates "unsweetened" or "no sugar added."

This list shows the different amounts of fruits to use for one fruit exchange.

	<i>Meas</i>	<i>Gm</i>
Apple	1 small (2" diam.)	80
Applesauce	$\frac{1}{2}$ cup	100
Apricots fresh	2 medium	100
Apricots dried	4 halves	20
Banana	$\frac{1}{2}$ small	80
Berries Straw * Rasp, Black	1 cup	150
* Blueberries	$\frac{2}{3}$ cup	100
Cantaloupe	$\frac{1}{4}$ (6" diam.)	200
Cherries	10 large	75
Dates	2	15
Figs fresh	2 large	80
Figs dried	1 small	15
* Grapefruit	$\frac{1}{2}$ small	120
* Grapefruit Juice	$\frac{1}{2}$ cup	100
Grapes	12	75
Grape Juice	$\frac{1}{4}$ cup	60
Honeydew Melon	$\frac{1}{4}$ (7" diam.)	150
Mango	$\frac{1}{2}$ small	70
* Orange	1 small	100
* Orange Juice	$\frac{1}{2}$ cup	100
Papaya	$\frac{1}{4}$ medium	100
Peach	1 medium	100
Pear	1 small	100
Pineapple	$\frac{1}{2}$ cup	80
Pineapple Juice	$\frac{1}{2}$ cup	80
Plums	2 medium	100
Prunes dried	2 medium	25
Raisins	2 Tbsp	15
* Tangerine	1 large	100
Watermelon	1 cup	175

For variety you can serve fruit as a salad or with unsweetened gelatin as a dessert.

* These fruits are rich sources of Vitamin C; use at least one serving each day.

BREAD EXCHANGES—LIST 4

One bread exchange contains 15 grams Carbohydrate, 3 grams Protein and 70 Calories.

For each bread exchange called for on your meal plan, choose any one item on the list below.

For example:

$\frac{1}{2}$ cup cooked cereal will give you 1 Bread Exchange.

1 slice bread and 1 small potato will give you 2 Bread Exchanges.

1 slice bread and $\frac{1}{2}$ cup cooked rice and $\frac{1}{4}$ cup corn will give you 3 Bread Exchanges.

This list shows the different amounts of foods to use for one bread exchange

	Meas	Gm
Bread	1 slice	25
Biscuit, Roll	1 (2 diam)	35
Muffin	1 (2 diam)	35
Cornbread	1 (1½ cube)	35
Flour	2¼ Tbsp	20
Cereal cooked	½ cup	100
Cereal dry (flake & puffed)	¼ cup	20
Rice Grits cooked	½ cup	100
Spaghetti Noodles etc cooked	½ cup	100
Crackers graham (2¼ sq)	2	20
Oyster	20 (½ cup)	20
Saltines (2 sq)	5	20
Soda (2¼ sq)	3	20
Round thin (1½ diam)	6-8	20
Vegetables		
Beans & Peas dried cooked	½ cup	90
(lima navy split pea cowpeas etc)		
Baked Beans no pork	¼ cup	50
Corn	½ cup	80
Larsoips	¾ cup	125
Potatoes white baked boiled	1 (2 diam)	100
Potatoes white mashed	½ cup	100
Potatoes sweet or Yams	¾ cup	50
Sponge Cake plain	1 (1½ cube)	25
Ice Cream (Omit 2 fat exchanges)	¼ pint	70

B

white crackers rice or spaghetti that do not have the vitamins added

MEAT EXCHANGES—LIST 5

One meat exchange contains 7 grams Protein 5 grams Fat and 70 Calories

You may have any kind of meat you wish Cheese eggs and peanut butter can be taken in place of meat for variety

For each meat exchange called for on your meal plan choose any one item on the list below

For example

1 Egg will give you 1 Meat Exchange

1 ounce Cheese and 1 ounce Ham will give you 2 Meat Exchanges

1 Egg and ¾ cup Cottage Cheese and 1 slice Bologna will give you 3 Meat Exchanges

This list shows the different amounts of foods to use for one meat exchange

	Meas	Gm
Meat & Poultry (med fat)	1 oz	80
(beef lamb pork liver chicken etc)		
Cold Cuts (1½ sq ½ thick)	1 slice	45
Frankfurter	1 (8-9 lb)	50
Fish Cod Mackerel etc.	1 oz	30
Salmon Tuna Crab	¾ cup	30
Oysters Shrimp Clams	5 small	45
Sardines	3 medium	30
Cheese cheddar American	1 oz	30
Cottage	¾ cup	45
Egg	1	50
Peanut Butter	2 Tbsp.	30

FAT EXCHANGES—LIST 6

One fat exchange contains 5 grams Fat and 45 Calories

All fat foods are high in calories. Too much fat or too much of any food may cause you to gain weight. A person with diabetes should try to reach his ideal weight. If he weighs too much his diabetes will be harder to control.

Use the foods on this list only as allowed on your meal plan.

You may use your fat exchanges in preparing such foods as vegetables and meats. For example, if you use a teaspoon of fat to fry an egg give up one fat exchange.

For each fat exchange called for on your meal plan choose any one item on the list below.

For example

1 teaspoon butter will give you 1 Fat Exchange

1 teaspoon margarine and 1 slice bacon will give you 2 Fat Exchanges

This list shows the different foods to use for one fat exchange

	<i>Meas</i>	<i>Gm</i>
<i>Butter or Margarine</i>	<i>1 tsp</i>	<i>5</i>
Bacon crisp	1 slice	10
Cream light 20%	2 Tbsp	30
Cream heavy 40%	1 Tbsp	15
Cream Cheese	1 Tbsp	15
French Dressing	1 Tbsp	15
Mayonnaise	1 tsp	5
Oil or Cooking Fat	1 tsp	5
Nuts	6 small	10
Olives	5 small	50
Avocado	$\frac{3}{8}$ (4 diam)	25

6 A familiarity with the means and advantages of a varied dietary. The recipes included in the patients' pamphlet as prepared by the American Diabetes and American Dietetic Associations are included in the prospect that they will be helpful as examples in this respect.

RECIPES

LEMON GELATIN

(May be used in any amount)

1 teaspoon unflavored gelatin
2 tablespoons cold water

1 tablespoon lemon juice
 $\frac{1}{2}$ cup water

Place in a small bowl and stand 10 minutes at room temperature. You wish you may add juice and $\frac{1}{2}$ cup coffee in place of $\frac{1}{2}$ cup water.

ORANGE GELATIN 1 Serving equals 1 Fruit from List 3

Use $\frac{1}{2}$ cup orange juice in place of water in recipe for lemon gelatin

PINEAPPLE GELATIN 1 Serving equals 1 Fruit from List 3

1 teaspoon unflavored gelatin

1 tablespoon lemon juice

$\frac{1}{4}$ cup cold water

$\frac{1}{5}$ cup pineapple juice

FRUIT GELATIN—I 1 Serving equals 1 Fruit from List 3

One serving of any fruit from List 3 may be added to lemon gelatin such as $\frac{1}{2}$ small banana.

FRUIT GELATIN—II 1 Serving equals 2 Fruits from List 3

One serving of any fruit from List 3 may be added to orange or pineapple gelatin

FRUIT ICE

1 Serving equals 1 Fruit from List 3

$\frac{3}{4}$ cup orange juice or $\frac{1}{2}$ cup pineapple juice

1 egg white

1 tablespoon lemon juice

$\frac{1}{2}$ cup water

Combine fruit juice and water and freeze. Stir mixture often while freezing. When almost hard fold in one stiffly beaten egg white.

FRESH FRUIT CUP

(1 Serving equals 1 Fruit from List 3)

Any fruits in List 3 may be combined to make a fruit cup. $\frac{1}{2}$ cup of mixed fruits equals 1 serving.

Example

Orange Grapefruit Pineapple

Peach Orange Blackberries

Apple Grapefruit Strawberries

Grapes Orange Melon

Melon Grapefruit, Banana

CANNING FRUIT WITHOUT SUGAR

(1 Serving equals 1 Fruit from List 3)

Any fruit—peaches, pears, etc. may be canned at home by following the usual directions for canning except that you omit the sugar. Can fruit in its own juice with enough water added to fill the jar. You will find directions in any cook book for the amount of time to steam the fruit. The fruit will keep all right if the can is properly sealed.

BAKED CUSTARD

1 Serving equals $\frac{1}{2}$ cup Milk and 1 Meat Exchange)

1 egg

Few grains salt

$\frac{3}{4}$ teaspoon vanilla

$\frac{1}{2}$ cup milk

Sprinkle of nutmeg

Beat the egg slightly, stir in milk, salt and vanilla. If you wish, add $\frac{1}{4}$ grain saccharin to flavor. Pour into a custard cup and sprinkle with nutmeg. Set in pan of hot water and bake in a moderate oven (350°) for about 45 minutes.

Other flavors such as almond, lemon, orange or maple may be used in place of vanilla.

CHEESE FONDLE

(1 Serving equals 1 Bread Exchange and 2 Meat Exchanges and 1 cup Milk)

1 egg

1 slice bread, cubed

1 cup milk

$\frac{1}{4}$ cup cheese, diced (1 oz.)

Salt, pepper, chopped parsley and onion

Beat the egg, add milk, bread, cheese and seasoning. Bake in a moderate oven (350°) until firm in the center, about 20 or 30 minutes.

In place of cheese, $\frac{1}{4}$ cup (1 oz.) of chopped ham, chicken, tuna fish or salmon may be used.

VEGETABLE SOUP

(1 Serving equals 1 Vegetable from List 2B)

1 cup meat stock or bouillon cube and 1 cup water

 $\frac{1}{2}$ cup mixed vegetables carrots, peas

1 stalk celery, diced

 $\frac{1}{2}$ small onion, chopped $\frac{1}{4}$ cup tomato juice $\frac{1}{4}$ cup cabbage shredded

Salt and pepper

Prepare vegetables and add to broth Boil together until vegetables are just tender about 20 minutes

POTATO SALAD A

(1 Serving equals 1 Bread Exchange)

 $\frac{1}{2}$ cup cooked potato diced

1 or 2 tablespoons Zero salad dressing

Salt, pepper, chopped onion celery, parsley, green pepper, as desired

Combine ingredients and serve

POTATO SALAD B

(1 Serving equals 1 Fat Exchange and 1 Bread Exchange)

Use same recipe as Potato Salad A except that 1 teaspoon of mayonnaise may be used in place of Zero salad dressing

POTATO SALAD C

(1 Serving equals 1 Bread Exchange and 1 Meat Exchange and 1 Fat Exchange if desired)

1 hard cooked egg, sliced, may be added to recipe for Potato Salad A or B

$\frac{1}{4}$ cup (1 oz) diced ham bologna or frankfurt, or 5 small shrimp may be used in place of egg

ZERO SALAD DRESSING

(May be used in any amount)

 $\frac{1}{2}$ cup tomato juice

1 tablespoon onion finely chopped

2 tablespoons lemon juice or vinegar

Salt and pepper

Chopped parsley or green pepper horseradish, or mustard etc., may be added if desired

Combine ingredients in a jar with a tightly fitted top Shake well before using

MEAT STEW

(1 Serving equals 2 or 3 Meat Exchanges and 1 Bread Exchange and 1 Serving Vegetable from List 2B and 1 Fat Exchange)

1 teaspoon fat

2 or 3 oz meat cubed

 $\frac{1}{2}$ cup mixed vegetables list 2B (carrots, peas onions)

1 small potato

Salt and pepper to taste

BAKED CHICKEN AND RICE

(1 Serving equals 1 Bread Exchange and 1 or 2 Meat Exchanges)

 $\frac{1}{2}$ cup cooked rice $\frac{1}{4}$ cup clear broth $\frac{1}{4}$ or $\frac{1}{2}$ cup diced chicken (1 or 2 oz)

Salt and pepper

Chopped parsley, onions, celery, mushrooms green pepper, pimiento or tomatoes may be added for variety, if desired

Combine the above ingredients and place in dish Bake in a moderate oven until brown

In place of rice you may use noodles or spaghetti For the chicken you may use any type of meat or fish, such as, lamb, ham, tuna or shrimp

FISH CHOWDER

(1 Serving equals 1 Fat Exchange and 1 Bread Exchange and 1 or 2 Meat Exchanges and 1 cup Milk)

1 teaspoon fat	$\frac{1}{4}$ or $\frac{1}{2}$ cup cooked fish (1 or 2 oz.)
$\frac{1}{2}$ small onion chopped	1 cup milk
1 small potato sliced	Salt and pepper

Cook fish in salted water. Melt fat in saucepan brown the onion. Add cooked fish sliced potato $\frac{1}{2}$ cup water in which fish was cooked. Cover and cook for 15 minutes until potatoes are tender. Add milk and seasonings.

ITALIAN SPAGHETTI

(1 Serving equals 1 or 2 Meat Exchanges and 1 or 2 Bread Exchanges and 1 Fat Exchange)

1 teaspoon fat	Salt pepper
$\frac{1}{2}$ small onion chopped	$\frac{1}{2}$ cup tomatoes
2 tablespoons tomato paste	1 or 2 oz. hamburger
$\frac{1}{2}$ cup water	$\frac{1}{2}$ cup cooked spaghetti

Brown the onion hamburger and fat. Add the tomato paste water and tomatoes. Allow to simmer gently one or more hours. If needed add more water. Serve on $\frac{1}{2}$ or 1 cup cooked spaghetti. 1 or 2 teaspoons grated cheese may be used.

MACARONI AND CHEESE

(1 Serving equals 1 Bread Exchange and 1 or 2 Meat Exchanges and $\frac{1}{4}$ cup Milk)

$\frac{1}{2}$ cup cooked macaroni	$\frac{3}{4}$ cup milk
$\frac{1}{4}$ or $\frac{1}{2}$ cup diced cheese (1 or 2 oz.)	Salt pepper dash of mustard

Cook cheese and milk together in double boiler until smooth. Add macaroni and mix well. Bake in moderate oven about 20 minutes or until brown.

In place of macaroni you may use $\frac{1}{2}$ cup cooked rice noodles or spaghetti.

MIXED VEGETABLE SALAD

(May be used in any amount)

Any combination of vegetables from List 2A may be used such as

- 1 Lettuce cucumber celery green pepper
- 2 Chicory tomato radish

1

- 7 Lettuce raw spinach radish

Salad may be combined with Zero Salad Dressing French Dressing or Mayonaise depending upon fat allowed in your meal plan.

MAKING THE MENU

Illustration Diet Prescription Protein 90 gm carbohydrate 210 gm fat 55 gm and 1700 calories (Standard diet No. V, p. 126)

Step 1 Divide the day's protein, fat and carbohydrate allowances into approximately three equal meals. * Example—

Protein	$90 \div 3 = 30$ gm
Fat	$55 \div 3 = 18$ to 19 gm
Carbohydrate	$210 \div 3 = 70$ gm

Step II Plan the menu for each meal

Example (a) List the foods desired for breakfast as designated in column A Table 16

* Unequal distribution of the diet is often indicated. This is discussed on pages 108 and 111 and illustrated in the standard diets on pages 122 to 132.

(b) Insert the exchange from which each food is taken as in column II and for convenience add the list number of each as in column C

TABLE 16
ILLUSTRATIVE MENU FOR BREAKFAST

A	II	C	D	E
Eggs	Meat exchange	list #5	2	2 eggs
Bread	Bread exchange	list #1	3	3 slices
Butter	Fat exchange	list #6	1	1 tsp
Milk	Milk exchange	list #1	1	1 cup
Fruit	Fruit exchange	list #3	1½	1½ serving

Step III Adjust the amounts (the number of exchanges) until they fill the total for each dietary component as in column D This procedure is expedited by completing the carbohydrate quota first, then the protein, and lastly the fat The foods and amount of each which are selected to use up the exchanges allowed are listed in column E The completed menu is presented in Table 17

TABLE 17
ILLUSTRATION OF COMPLETED MENU

	NO EXCHANGES	HOUSEHOLD MEASURE	WEIGHT GRAMS	P	F	C
<i>Breakfast</i>						
Meat	2	2 eggs		14	10	—
Bread	3	3 sl	75	6	—	45
Fat	1	1 tsp	5	—	5	—
Milk skim	1	1 c	240	8	—	12
Fruit	1½	1½ serv	See list 3	—	—	15
				28	15	72
<i>Lunch (or supper)</i>						
Meat	2	2 oz	60	14	10	—
Bread	3	3 sl	75	6	—	45
Fat	2	2 tsp	10	—	10	—
Vegetable	2A	1 serv	100	—	—	—
Vegetable	2B	1 serv	100	2	—	7
Milk skim	1	1 c	240	8	—	12
Fruit	1	1 serv	See list 3	—	—	10
				30	20	74
<i>Evening or (Main Meal)</i>						
Meat	3	3 oz	90	21	15	—
Bread	3	3 sl	75	6	—	45
Fat	1	1 tsp	5	—	5	—
Vegetable	2A	1 serv	100	—	—	—
Vegetable	2B	1 serv	100	2	—	7
Fruit	1½	1½ serv	See list 3	—	—	15
				29	20	67
Day's Total				87	55	213

STANDARD DIETS

Standard diets as indicated in Table 18, and greatly in simplifying the treatment of diabetic patients. For uncomplicated diabetes they serve admirably but they should not be used at the expense of more intensive individualization which may be highly desirable during the course of complicating diseases, e.g. duodenal ulcer, hepatitis, etc. The diet prescription may be suitable in such cases but the food components and the distribution of the diet are altered to meet the individual's needs and appropriate changes are made in the insulin therapy to maintain good control of the diabetes.

Maximum usefulness of the standard diets will be obtained (a) when the prescription for the diet is arrived at as outlined on pages 106 to 108 and (b) when full advantage is taken of the flexibilities permitted by the various food exchanges. In the illustrative standard diets (pages 122 to 132) a "food exchange" column is included to simplify the substitution of suitable foods for those indicated in the sample menu.

TABLE 18
STANDARD DIET PRESCRIPTIONS

	PROTEIN	CARBOHYDRATE	FAT	CALORIES
I	75	100	22	900
II	80	120	33	1100
III	85	130	49	1300
IV	90	180	47	1500
V	90	210	53	1700
VI	90	210	69	1900
VII	95	260	74	2100
VIII	95	280	89	2300
IX	100	300	100	2500
X	110	320	109	2700
XI	120	335	120	2900

Eleven standard diet prescriptions are listed in this table. Diets III, IV, V and VI are suitable for the initial treatment in the majority of cases and for the more permanent programs diets VI, VII and VIII suffice for the majority of the adult patients. It will be noted that (a) the protein and carbohydrate allowances in the more permanent diets are more liberal than formerly used and (b) the fat content is kept below 100 grams except in the three high caloric diets.

The standard diets Nos. I to IV inclusive—providing 900, 1100, 1300 and 1500 calories respectively—are used in the treatment of overweight patients having mild diabetes. These patients do not need insulin and they are at liberty to save any part of any meal to be taken between meals or at bedtime if desired. It is inadvisable on the other hand to take only two big meals in the day or two very small meals and one large meal.

The more liberal diets—from 1700 to 2900 calories—are commonly used by patients taking insulin in which case there are specific indications for a distribution of the diet which gives maximum advantage to the respective insulin therapy. This feature has been dealt with already in detail (p. 103).

Diet No 1—900 CALORIES
Protein 75 gm, Fat 22 gm, Carb 100 gm
Division of diet approximately $\frac{1}{3}$ for each meal with a bedtime nourishment

NO EXCHANGES	FOOD EXCHANGE	LIST NO	SAMPLE MENU	HOUSEHOLD MEAS	WT GM	F	F	C	CAL
Breakfast									
2	Meat	5	Eggs	2		14		10	146
1	Bread	4	Bread	1 sl	25	2		—	68
1	Fruit	3	Orange	1 sm	100	—		—	40
$\frac{1}{4}$	Milk	1	Skim milk	$\frac{1}{4}$ c	60	2		3	20
			Total			18	10	28	274
Lunch (or Supper)									
3	Meat	5	*Roast beef (lean)	3 oz	90	21		9	165
1	Bread*	4	Bread	1 sl	25	2		—	68
1	Vegetable	2A	String beans, young	$\frac{1}{2}$ c	100	—		—	—
$\frac{1}{4}$	Milk	1	Skim milk	$\frac{1}{2}$ c	120	4		6	40
1	Fruit	3	Peach	1 med	100	—		10	40
			Total			27	9	31	313
Dinner (or Main Meal)									
3	Meat	5	Broiled liver	2 oz	60	14		6	110
$\frac{1}{4}$	Bread	4	Bread	$\frac{1}{2}$ sl	13	1		8	26
1	Vegetable	2A	Lettuce and cucumber		100	—		—	—
1	Milk	1	Skim milk	1 c	210	8		12	80
1	Fruit	3	Strawberries	1 c	150	—		10	40
			Total			23	6	30	266
Nourishment									
1	Milk	1	Skim milk	1 c	210	8		12	80
			Days total			76	25	101	933

* Visible fat removed

Note sm—small, med—medium, lg—large, oz—ounce, tsp—teaspoon, tsp—tablespoon, c—cup, sl—slice

This low calorie diet (900 calories) is used as a temporary measure to permit a reduction in the weight of the obese diabetic patient. A nourishment has been taken from the total diet for use at bedtime. Ordinarily patients receiving this diet are not taking insulin.

Diet No. II—2100 Calories
 Protein 80 gm Fat 33 gm Carb 120 gm
 Division of diet approximately 15 for each meal with a bedtime nourishment

NO	FOOD	LIST	SAMPLE MENU	HOUSEHOLD	WT	P	P	D	CAL
EXCHANGE	EXCHANGE	NO		MEAS	CM				
Breakfast									
2	Meat	5	Lean	2	25	14	10	—	146
1	Bread	4	Bread	1 d	—	2	—	15	60
1½	Milk	1	Skim milk	¾ c	180	6	—	9	60
1	Fruit	3	Cantaloupe	1½ med	200	—	—	10	40
			Total			22	10	34	314
Lunch (or Supper)									
—	Meat	5	Cottage Cheese	1½ c	90	14	10	—	146
1	Vegetable	2A	Tomato and lettuce	1	100	—	—	—	—
1	Bread	1	Muffin	1	35	2	—	15	68
1½	Milk	1	Skim milk	¾ c	180	6	—	9	60
1	Fruit	3	Apple sauce	1½ c	100	—	—	10	40
			Total			22	10	34	314
Dinner (or Supper)									
3	Meat	5	Roast Lamb	1 oz	90	21	15	—	219
1	Vegetable	2A	Spinach	¾ c	100	—	—	—	—
1	Vegetable	2B	Pickled beets	¾ c	100	2	—	7	36
1	Bread	1	Bread	1 d	25	2	—	15	68
1	Fruit	3	Apples	2 med	100	—	—	10	40
			Total			25	15	32	363
Nourishment									
1	Milk	1	Skim milk	1 c	210	8	—	12	80
1½	Bread	1	Graham cracker	1	10	1	—	8	36
			Total			9	—	20	116
			Day's Total			78	35	120	1107

For key to abbreviations see footnote, p 122

As in the case of the first diet (900 calories) this diet—1100 calories—is also employed to reduce body weight of obese diabetic patients. A nourishment, deducted from the total diet is taken at bedtime. Ordinarily this diet is not supplemented with insulin therapy

Diet No. III—1300 CALORIES
Protein 85 gm., Fat 49 gm., Carb 130 gm.
Division of diet approximately $\frac{1}{3}$ for each meal with a bedtime nourishment

NO	FOOD	LIST	HOUSEHOLD	WT	P	F	E	CAL
EXCHANGES	EXCHANGE	NO	MEAS	GR				
Breakfast								
2	Meat	B	Eggs	2	14	10	—	146
1	Bread	4	1 sl	25	2	—	15	68
1	Milk	1	1 c	210	8	—	12	80
1	Fruit	1	$\frac{1}{2}$ sm	125	—	—	10	40
1	Fat	6	1 tsp	5	—	5	—	45
			Total		24	15	37	379
Lunch (or Supper)								
2	Meat	2	Cheese	2 oz	14	10	—	146
1	Milk	1	Skim milk	1 c	8	—	12	80
1	Vegetable	2A	Asparagus and lettuce	$\frac{1}{2}$ c	—	—	—	—
1	Bread	4	Bread	100	2	—	15	68
1	Fat	6	Mayonnaise	1 sl	—	5	—	45
1	Fruit	3	Peach	1 tsp	—	—	10	40
			Total		24	15	37	379
Dinner (or Main Meal)								
3	Meat	5	Roast chicken	3 oz	21	15	—	219
1	Vegetable	2A	Cabbage	$\frac{1}{2}$ c	—	—	—	—
1	Vegetable	2B	Peas green	$\frac{1}{2}$ c	2	—	7	36
1	Bread	4	Potato	1 sm	2	—	15	68
1	Fat	6	Butter	1 tsp	—	5	—	45
1 $\frac{1}{2}$	Fruit	3	Plums	3 med	—	—	15	60
			Total		25	20	37	428
Nourishment								
1	Milk	1	Skim milk	1 c	8	—	12	80
1 $\frac{1}{2}$	Bread	4	Saltines	2-3	1	—	8	36
			Total		9	—	20	116
			Days Total		82	50	131	1302

See key to all revisions see footnote p 122

Diet No. III is employed to reduce the body weight of obese diabetic patients who having acute complications are not receiving insulin

DIET No IV—1500 CALORIES
 Protein 100 gm, Fat 47 gm Carb 180 gm
 Division approx 1/5 for each meal with a bedtime nourishment

NO	FOOD	LIST	SAMPLE	MPD	HOLD	WT	P	F	C	CAL.
EXHIBITS	REMARKS	NO				GM				
Breakfast										
1	Ment	5	Eggs	2		25	14	10	—	146
2	Bread	4	Bread	1 1/2 c		100	—	—	15	68
			Oatmeal	1 c		210	8	—	18	68
1	Milk	1	Milk skim	1 c		5	—	5	—	45
1	Fat	6	Butter	1 tsp		100	—	—	10	40
1	Fruit	3	Grapefruit juice	1/2 c			26	15	52	147
			Total							
Lunch (or Supper)										
1	Ment	5	Frankfurter	2		100	14	10	—	116
1	Milk	2	Milk skim	1 c		210	8	—	12	111
1	Vegetable	2A	Sauerkraut	1/2 c		100	—	—	—	—
2	Bread	4	Rolls	2 am		70	4	—	30	136
1	Fat	6	Butter	1 tsp		5	—	5	—	11
1	Fruit	3	Applesauce	1/2 c		100	—	—	10	40
			Total				26	15	52	147
Dinner (or Main Meal)										
3	Ment	5	Roast lamb	3 oz		90	21	15	—	219
1	Vegetable	2A	Chard	1/2 c		100	—	—	—	—
1	Vegetable	2B	Carrot strips	1/2 c		100	2	—	7	36
2	Bread	4	Potato	1 am		100	2	—	15	68
			Bread	1 al		25	2	—	15	60
1 1/2	Fruit	3	Watermelon	1 1/2 c		260	—	—	15	60
			Total				27	15	52	151
Nourishment										
1	Milk	1	Milk, skim	1 c		210	8	—	12	111
1	Bread	4	Graham crackers	2		20	2	—	15	68
			Total				10	—	27	118
			Day's Total				89	45	183	1193

For key to abbreviations see footnote, p 122

Diet No IV is employed temporarily when a slow or slight reduction in weight is indicated. Insulin therapy may or may not be used in connection with this diet.

DIET NO. V-1/100 CALORIES
 Protein 90 gm Fat 57 gm Carb 210 gm
 Division approx 1/3 of diet for each meal*

NO	FOOD	LIST NO	SAMPLE MENU	HOUSEHOLD MEAS	WT GM	P	F	C	GAL
Breakfast									
2	Meat	5	Eggs	■		14	10	—	116
1	Fat	6	Butter	1 tsp	5	—	5	—	45
3	Fruit	3	Banana	1 sm	100	—	—	20	80
2 1/2	Bread	4	Bread	1 1/2 sl	38	3	—	23	101
				3/4 c	20	■	—	15	68
1	Milk	1	Wheatena	1 c	210	8	—	12	80
			Total			27	15	70	523
Lunch (or Supper)									
3	Meat	5	Egg	1		7	5	—	73
1	Milk	1	Tuna	1/2 c	60	14	10	—	116
1	Vegetable	2A	Milk skim	1 c	210	8	—	12	80
1	Vegetable	2B	Lettuce	1 1/2 head	100	—	—	—	—
1	Bread	4	Pickled beets	1 1/2 c	100	2	—	7	108
1	Fat	6	Bread	2 sl	50	1	—	30	136
2	Fruit	3	Butter	1 tsp	5	—	5	—	45
			Tangerine	2 lg	200	—	—	20	80
			Total			35	20	69	596
Dinner (or Main Meal)									
2	Meat	5	Mackerel	2 oz	60	14	10	—	146
1	Vegetable	2A	Spinach	1/2 c	100	—	—	—	—
1	Vegetable	2B	Onions	100	—	2	—	7	36
1	Fat	6	Oil	1 tsp	■	—	5	—	45
2	Fruit	■	Apricots	4 med	200	—	—	20	80
3	Bread	4	Potato	2 sm	200	4	—	30	136
			Bread	1 sl	25	2	—	15	68
1	Meat	■	Egg	1	—	7	5	—	73
			Total			29	20	72	581
Days Total									
						91	55	211	1701

* Though this diet is divided into approximately three equal meals a milk and a bread exchange are indicated in List type in the breakfast and in the dinner menus. One or both of these designated nourishments can be deducted from the respective meal given at other times of the day in keeping with the insulin therapy as outlined on pages 108 to 111. The same provision is made in the subsequent diets VI to XI for key to all abbreviations see footnote p. 122

Diet No. 31—1900 Calories
 Protein 90 gm Fat 69 gm Carb 230 gm
 Division approx 1/5 of diet for each meal

NO	FOOD	LIVESTOCK	HOUSEHOLD	WT	P	F	M	CAL.
EXCHANGES	FRAGRANCE	NO	SAMPLE MEAT	MEAT	P	F	M	CAL.
Breakfast								
2	Meat	5	Eggs	—	14	10	—	116
2	Fat	6	Butter	2 1/2 cup	—	10	—	90
2	Fruit	3	Orange juice	1 c	—	—	20	80
2	Bread	1	Bread	2 sl	3	—	30	136
1	Milk	1	Milk, skims	1 sl	8	—	15	68
				210	—	—	12	80
			Total		28	20	47	600
Lunch (or supper)								
2	Meat	5	Oysters	10	14	10	—	116
1	Milk	1	Milk, skims	1 c	8	—	12	80
1	Vegetable	2 sl	Mixed vegetable salad	1/2 c	—	—	—	—
2	Bread	1	Oyster crackers	1/2 c	3	—	15	68
3	Fat	1	Bread	2 sl	4	—	30	136
1	Fruit	6	Butter	3 1/2 cup	—	15	—	135
		3	Peach	4 halves	—	—	20	80
			Total		28	25	77	615
Dinner (or Main Meal)								
2	Meat	5	Steak	2 oz	15	10	—	116
2	Vegetable	2 sl	Tomato sliced	1	—	—	—	—
1	Vegetable	6	Peas, green	1/2 c	2	—	7	36
2	Fat	3	Butter	2 1/2 cup	—	10	—	90
1	Fruit	—	Peas	1 can	—	—	10	80
4	Bread	—	Bread	3 sl	6	—	15	68
1	Milk	5	Bread	2 sl	2	—	12	80
			Cheese	1 oz	7	5	—	73
			Total		31	25	77	637
			Day's Total		87	70	231	1902

Footnote p. 126
 or key to abbreviations see footnote p. 122

Diet No VII—2100 Calories
 Protein 95 gm. Fat 75 gm. Carb 260 gm
 Division approx 1/3 of diet for each meal*

NO EXCHANGES	FOOD EXCHANGE	LIST NO	SAMPLE MENU	HOUSEHOLD MEAS	WT GM	F	F	E	CAL.
Breakfast									
2	Meat	5	Eggs	2	—	11	10	—	146
1	Fat	6	Butter	1 tsp	5	—	5	—	15
1 1/2	Fruit	3	Prunes	3 med	38	—	—	15	60
4	Bread	4	Bread	3 sl	75	6	—	45	204
			Bread	1 sl.	25	2	—	15	60
1	Milk	1	Milk, whole	1 c	240	8	10	12	170
			Total			30	25	87	693
Lunch (or Supper)									
2	Meat	5	Cold cuts	2 sl	90	14	10	—	116
1	Milk	1	Milk, whole	1 c	210	8	10	12	170
1	Vegetable	2A	Lettuce and cucumber	1 1/2 c	100	—	—	—	—
1	Vegetable	2B	Carrots	3/4 c	100	2	—	7	36
3	Bread	4	Bread	3 sl	75	6	—	15	204
1	Fat	6	Butter	1 tsp	5	—	5	—	15
2	Fruit	3	Grapes	24	150	—	—	20	80
			Total			30	25	84	681
Dinner (or Main Meal)									
3	Meat	5	Chicken	3 oz	90	21	15	—	219
1	Vegetable	2A	String beans, young	3/4 c	100	—	—	—	—
1	Fat	6	Butter	1 tsp	5	—	5	—	15
1	Vegetable	2B	Winter squash	3/4 c	100	2	—	7	45
2	Fruit	3	Pineapple	1 c	160	—	—	20	36
4	Bread	4	Discuits	1	105	6	—	45	100
			Bread	1 sl.	25	2	—	15	204
1	Meat	5	Eggs	1	—	7	—	—	60
			Total			38	25	87	733
			Day's Total			98	75	218	2099

* See footnote, p 126
 1 or key to abbreviations on footnote p 122

Diet No. VIII—2000 CALORIES
 Protein 95 gm Fat 80 gm Carb 280 gm
 Division approx 1/5 of diet for each meal*

NO	FOOD	LINE	MEAT	VEGETABLES	FRUIT	GRAIN	P	F	C	CAL
Breakfast										
2	Meat	5		Eggs	2	10	10			146
2	Fat	6		Butter	2 am	10	10			90
3	Fruit	3		Orange	3 am			20		80
4	Bread	4		Bread	3 am		6		15	204
				Butter	1/2 c		8		15	100
1	Milk	1		Milk, whole	1 c	10	10	12		170
				Total		30	10	92		758
Lunch (or Supper)										
2	Meat	5		Corn meat	1/2 c	10	10			146
1	Milk	1		Milk, whole	1 c	10	10	12		170
1	Vegetable	2A		Tomato juice	3/2 c					
1	Vegetable	2B		Peas, green	3/2 c		2	7		36
1	Bread	3		Bread	4-3		8	60		272
1	Fat	6		Butter	2 tsp	10	10			90
3 1/2	Fruit	3		Banana	5/8 am			15		60
				Total		32	30	93		774
Dinner (or Main Meal)										
2	Meat	5		Lamb chops	2 am	10	10			146
1	Vegetable	2A		Lettuce	1 1/2 head					
1	Vegetable	2B		Beets	3/2 c		2	7		36
3	Fruit	4		Butter	2 tpp	10	10			90
				French dressing	1 tpp	5				15
1	Fruit	3		Cherries	10 lg			10		10
1	Bread	4		Bread	3 ad		6	15		204
				Lima beans	3/2 c		8	15		100
				Walla crackers	3		2	15		68
1	Meat	5		Cherese	1 oz.	5	5			73
				Total		33	30	92		770
				Day's Total		93	90	278		2502

footnote p 126
 Key to abbreviations see footnote, p 122

Diet No. IV—2500 CALORIES
Protein 100 gm Fat 100 gm Carb 300 gm
Division approx. 1/3 of diet for each meal*

NO	FOOD	LIST	SAMPLE MENU	HOUSEHOLD	WT	P	F	C	CAL.
EXCHANGES	FXCHANGE	NO		MEAS	GM				
Breakfast									
2	Meat	5	Eggs	2	—	14	10	—	146
3	Fat	6	Butter	3 tsp	15	—	15	—	135
2	Fruit	3	Orange juice	1 c	200	—	—	20	80
	Bread	4	Bread	3 1/2 sl	87	7	—	53	210
	Milk	1	Maltex	1/2 c	100	2	—	15	68
			Milk, whole	1 c	210	8	10	12	170
			Total			31	35	100	839
upper)									
	Meat	5	Cold beef	2 oz	60	14	10	—	146
	Milk	1	Milk, whole	1 c	210	8	10	12	170
1	Vegetable	2A	Escarole raw	1 1/2 c	100	—	—	—	—
1	Vegetable	2B	Carrots	1 1/2 c	100	—	—	—	—
4	Bread	4	Bread	4 sl	100	3	—	7	36
	Fat	6	Butter	3 tsp	15	8	—	60	272
	Fruit	3	Applesauce	1 c	200	—	15	—	135
			Total			32	35	99	839
in Meal)									
	Meat	5	Roast pork	2 1/2 oz	75	17	12	—	176
	Vegetable	2A	Cole slaw	1 1/2 c	100	—	—	—	—
	Vegetable	2B	Peas green	1 1/2 c	100	—	—	7	36
1	Bread	4	Biscuits	2	70	4	—	30	136
	Fat	6	Sweet potato	1 1/2 c	100	4	—	30	136
3	Fruit	3	Butter	3 tsp	15	—	15	—	135
1	Milk	5	Grapes	2 1/2	150	—	—	20	80
1	Bread	4	Cottage cheese	1/4 c	—	7	5	—	73
			Saltines	5	20	8	—	13	68
			Total			36	32	102	810
			Day's Total			99	102	301	2,518

* See footnote p 126

For key to abbreviations see footnote p 122

Diet No. X—2000 Calories
Protein 110 gm Fat 100 gm Carb 320 gm
Division approx 1/3 of diet for each meal*

NO	FEEDING	PROG	LIVE	SAMPLE MENU	HOUSEHOLD	WT	P	F	C	CAL.
EXCHANGES	NO				MEALS	CM				
Breakfast										
1	Meat	5		Eggs	2	—	14	10	—	116
2	Fat	6		Butter	3 tsp	15	—	15	—	135
3	Fruit	3		Grapefruit	1 gm	200	—	—	20	80
4	Bread	1		Bread	4 dl	100	8	—	60	272
5				Cheerio	1/4 c	20	2	—	15	68
1	Milk	1		Milk, whole	1 c	210	8	10	12	170
				Total			32	35	107	871
Lunch (or supper)										
3	Meat	5		Tuna	1/4 c	90	21	15	—	219
1	Milk	1		Milk, whole	1 c	210	6	10	12	170
1	Vegetable	2 1/2		Celery and lettuce	1/2 c	100	—	—	—	—
1	Vegetable	2 1/2		Onions	1/2 c	100	2	—	7	36
4 1/2	Bread	1		Bread	1 dl	100	8	—	60	272
				Saltine	2 1/2	10	1	—	8	36
2	Fat	6		Butter	2 tsp	10	—	10	—	—
2	Fruit	3		Apples	4	200	—	—	20	—
				Total			40	35	107	903
Dinner (or Main Meal)										
2	Meat	5		Lamb chops	2 gm	60	14	10	—	146
1	Vegetable	2 1/2		Lettuce and chives	1 1/2 c	100	—	—	—	—
1	Vegetable	2 1/2		Rutabaga	1 1/2 c	100	2	—	7	36
5	Fat	6		Butter	5 tsp	25	—	20	—	223
1	Fruit	3		Apple	1/2 c	100	—	—	10	40
6	Bread	1		Bread	3 dl	25	6	—	15	261
				Potato, washed	1 c	200	1	—	30	136
1	Meat	5		Graham crackers	1/4 c	20	2	—	15	68
				Cottage cheese	1/4 c	15	7	5	—	73
				Total			33	40	107	928
Days total							107	110	321	2702

* See footnote p 126
or Any 10 of observations see footnote p 122

Diet No XI—2900 CALORIES
 Protein 120 gm Fat 120 gm Carb 335 gm
 Division approx $\frac{1}{3}$ of diet for each meal*

NO	EXCHANG	FOOD	LIST	SAMPLE MENU	HOUSEHOLD	WT	P	H	■	CAL
EXCHANG	CP	EXCHANG	NO		MEAS	GM				
Breakfast										
2		Meat	5	Eggs	2	—	14	10	—	116
1		Fat	6	Butter	3 tsp	15	—	15	—	135
1		Fruit	3	Prunes	4	50	—	—	20	80
3		Bread	4	Bread	4 J	100	8	—	60	272
1½		Milk	1	Rice Krispies	¾ c	20	2	—	15	60
				Milk, whole	1½ c	160	12	16	18	255
				Total			36	40	113	956
Lunch (or Supper)										
3		Meat	5	Coll cuts	2 sl	90	14	10	—	146
1		Milk	1	Cheese American	1 sl	30	7	5	—	73
1		Vegetable	2A	Milk whole	1 c	210	8	10	12	170
1		Vegetable	2B	Lettuce and cucumber	½ c	100	—	—	—	—
5		Bread	4	Beets	5 sl	125	2	—	7	111
3		Fat	6	Bread	3 tsp	15	10	—	75	340
2		Fruit	3	Butter	1 sm	100	—	15	—	135
				Banana			—	—	20	80
				Total			41	10	111	980
Dinner (or Main Meal)										
3		Meat	5	Liver	3 oz	75	21	15	—	219
1		Vegetable	2A	Tomatoes	½ c	100	—	—	—	—
1		Vegetable	2B	Onions	½ c	100	2	—	7	36
1		Fat	6	Butter	4 tsp	20	—	20	—	180
1		Fruit	3	Orange sliced	1	100	—	—	10	40
6		Bread	4	Noodles	½ c	100	2	—	15	68
1		Ment	5	Bread	3 sl	75	6	—	40	201
				Sponge cake	1½ cube	25	2	—	15	68
				Saltines	5	20	11	—	15	68
				Cheese	1 oz	30	7	11	—	73
				Total			42	40	107	956
				Day's Total			119	120	334	2992

* See footnote # 126
 1 or key to all brackets as in footnote # 122

CHAPTER XIV

Insulin Therapy

Introduction. In the contemplation of insulin therapy the following considerations will apply

- (a) Salient features governing insulin need
- (b) Is insulin therapy advisable and, if so,
- (c) Which insulin preparation or combination of insulin therapies is indicated what is the correct timing of the administration of the insulin in relation to meals how is the proper dosage determined and under what circumstances is the insulin regimen changed?
- (d) Administration of insulin

A SALIENT FEATURES GOVERNING THE NEED FOR INSULIN

Familiarity with the various insulin preparations and the rate, degree and duration of their respective activities is necessary for the proper selection and the most effective combinations of insulins for the individual patient. Individualization is the essence of insulin therapy. No two patients

TABLE 19
ALTERATIONS IN DIET AND THE CHANGING NEED FOR INSULIN

PROTEIN (GM)	FAT (GM)	CARBOHYDRATE (GM)	CALORIES	G.E. (GM)
80	120	150	2000	208
80	70	Diet changed to 280	2000	333

Increases in the carbohydrate and the theoretical glucose equivalent of the diet, as illustrated, cause only a minor increase in the need for insulin so long as the total calories are not increased (G.E. = glucose equivalent)

may require the same dose of insulin. Unlike most drug therapies the individual's need for insulin is determined by several factors and it is only after the amount of insulin given is adjusted to conform with the individual's "need pattern" that the diabetes is controlled. Too often one hears the loose remark that one unit will "look after" a certain number of grams of glucose. The insulin need does not conform to any such exact equivalent

and the claim that it does indicates a failure to understand the multitude of influences which determine the amount of insulin a patient may need. In order to emphasize some fundamental dietary factors which affect the insulin need clinically, several illustrative studies are offered.

First, a diet of 80 gm protein, 120 gm fat and 150 gm carbohydrate, giving a total value of 2000 calories (theoretical glucose equivalent or G E = 58 per cent of protein + 100 per cent of carbohydrate + 10 per cent of fat = 208 grams) may be allowed (see Table 19). Let us assume that with this diet 60 units of insulin are necessary to control the diabetes. The dosage of insulin having been established, an abrupt change in the diet is made to 80 gm protein, 280 gm carbohydrate and 70 gm fat—2000 calories (G E = 333 gm). It will be observed that the glucose equivalent has been increased from 208 to 333 gm but the total calories have been kept constant by reducing the fat content of the diet. If the insulin need fluctuated only with the amount of carbohydrate allowed in diet, an increase of 60 per cent—or a dosage of 96 units—would be needed to con-

TABLE 20
ALTERATIONS IN DIET AND THE CHANGING NEED FOR INSULIN

PROTEIN (GM)	FAT (GM)	CARBOHYDRATE (GM)	CALORIES	G E (GM)
80	120	150	2000	208
80	120	Diet changed to 280	2520	338

Increases in the carbohydrate and total calories as illustrated cause relatively great increases in the insulin need.

control the diabetes as efficiently as 60 units had done previously. This is not what happens. With the abrupt increase in the carbohydrate of the diet some glycosuria and hyperglycemia usually occur, but, these changes are small and are readily overcome by the addition of only a few units of insulin. Why is this so? The reason is that the total calories were kept unchanged and the only reason why there was any increase in the insulin dosage at all is that carbohydrate has stronger glycosuric and hyperglycemic effects than the caloric equivalent of fat.^{1, 2}

A second phenomenon and one of equal clinical significance is illustrated. Had the initial diet in Table 20 (P. 80 gm, F. 120 gm, and C. 150 gm—2000 calories) been changed by merely adding the 130 grams of carbohydrate (520 calories) provided by it to make the new diet 80 gm protein, 120 gm fat, and 280 gm carbohydrate—2520 calories, the increase in insulin necessary to control the diabetes

would be great. When the carbohydrate increase was accompanied by a reduction in fat. Combining these two phenomena it is observed that the total calories profoundly affect the insulin dosage and the carbohydrate allowance of the

diet can be greatly increased with only minor changes in the insulin need resulting, provided the total calories are not increased also

A third phenomenon and one of utmost importance, clinically, can be illustrated if a diet of protein 80 gm, fat 120 gm, carbohydrate 150 gm—2000 calories (theoretical glucose equivalent 208 gm) is replaced by a diet with approximately the same theoretical glucose equivalent but with a reduced total calories e.g., protein 80 gm, fat 50 gm, carbohydrate 155 gm, 1400 calories (G.E. 207 gm) (See Table 21) If the dietary influence on insulin need were confined to carbohydrate no change in the insulin need would ensue This is not what happens There is a remarkable reduction in the insulin need The initial reduction is due to the reduced

TABLE 21
ALTERATIONS IN DIET AND THE CHANGING NEED FOR INSULIN

PROTEIN (GM)	FAT (GM)	CARBOHYDRATE (GM)	CALORIES	G.E. (GM)
80	120	150	2000	208
80	50	Diet changed to 155	1400	207

Reduction of the total calories by reducing the fat but without appreciably altering the glucose equivalent as illustrated causes a marked reduction in the need for insulin

calories With progressive loss of weight and reduction in the total metabolism, there is also a progressive reduction in the insulin need

The foregoing phenomena, reproducible at will indicate that

1 Carbohydrate has a greater insulin demand than the caloric equivalent of fat.

2 The insulin need is governed to a large extent by the total caloric value of the diet

3 The combination of a low calorie diet and a reduction in body weight by reducing the total tissue metabolism exerts a profound insulin-sparing action

4 The combination of a diet sufficiently high in calories to add to the body weight exerts an increase in the need for insulin which is progressive until the diet is reduced or until the body weight becomes stabilized This effect on the insulin is by virtue of the large amount of food plus the increased total metabolism that accrues with a gain in body mass

5 Similarly complications affect total metabolism and in doing so affect the insulin requirement All influences which increase the total metabolism with but one exception—physical exercise—increase the need for insulin These are increased caloric intake, obesity, infections, fevers, toxemias, pregnancy and thyrotoxicosis Contrariwise, all influences which reduce the total metabolism with but one exception—the cessation of phys-

cal exercise—reduce the need for insulin. These are reduction in caloric intake, reduction in weight, correction of infections, fevers and toxemias, termination of pregnancy and the control or cure of thyrotoxicosis.

The protein content of the diet is not subject to the great fluctuation observed in the fat and carbohydrate contents and also its effect on the insulin requirement is feeble in contrast to that of carbohydrate and total calories.

B. IS INSULIN THERAPY ADVISABLE?

Insulin therapy is indicated *at once in all*

- 1 Diabetic children
- 2 Underweight adults who have glycosuria and hyperglycemia
- 3 Patients having acute complications, whether the underlying diabetes is mild or not, if there is glycosuria or hyperglycemia at any time in the twenty four hours

4 Cases of pregnancy complicating diabetes

5 Patients with a history of a sudden onset of symptoms of diabetes within the three months prior to the consultation. This applies to the patient with apparently mild diabetes who will obviously do well without insulin eventually, as well as to the patient with an obviously severe diabetes.

Insulin therapy is indicated in the treatment for diabetes when this disorder is not or obviously will not be, controlled satisfactorily by suitable dietetic measures and exercise and during acute complications for all diabetic patients, many of whom under usual circumstances may not need it. Some authorities give insulin, in the initial days of treatment, to all diabetic patients. In favor of this plan is the more rapid control of the diabetes and the training of the patient in the administration of insulin while he is under competent supervision. It also emphasizes that many patients can discontinue insulin. The majority of diabetic patients have a mild diabetes and ultimately do not need insulin. This information has a good effect in neutralizing a general and erroneous belief that once one uses insulin he must always use it. Unfortunately this is usually true for the thin patient having severe diabetes, but it is not true for obese patients who have mild diabetes.

All patients who have an acute onset of the diabetes, which may be mild or severe, should be given insulin with the hope that some may be cured. These rare individuals are the young or the thin patients with severe diabetes who are ordinarily given insulin from the outset of treatment. The obese, untreated diabetic patient has a mild diabetes which develops insidiously when the body mass has increased to such an extent and has been maintained for a sufficient period to exhaust an already reduced pancreatic reserve.

The amount of insulin needed is not relative to the degree of hyperglycemia with any constancy, nor can it be calculated with any degree of exactness according to the amount of sugar in the urine. If glycosuria exists in the case of a patient taking insulin, more insulin is needed, but what 5 units will do in ridding the urine of sugar in one patient may require 25, or more, units in another.

It is a good working rule, barring acute complications which will be considered later, that *all untreated diabetic patients who are considerably overweight will not need insulin notwithstanding the presence of a high fasting blood sugar level on the first examination.* Every physician who sees many diabetic patients has seen fat patients with blood sugar levels above 300 mg per 100 cc and yet insulin was not necessary to control their diabetes.

It is a good working rule, too, that *all children and underweight diabetic patients require insulin even if the initial level for fasting blood sugar should not be high.* The certainty that insulin will be needed by growing children and underweight adults is based on the knowledge that to promote normal health and physical growth, a gain in weight and a liberal diet, each of which increase the need for insulin, are necessary. The combination of a persistently elevated fasting blood sugar level and undernutrition makes insulin therapy imperative if good health is to be restored. It has been our practice at the Pennsylvania Hospital never to give insulin to overweight diabetic patients unless during some acute complication and unless there has been a recent sudden onset of the diabetes. The merit for the control of the diabetes should go to the dietetic measures and not to a preliminary and temporary course of insulin treatment. In this manner the patient can be deeply impressed by the value of a restricted diet. Approximately 40 per cent of the patients currently attending the metabolic clinic at the Pennsylvania Hospital do not need insulin. We have observed the effect of insulin on obese diabetic patients at other clinics and, for the purposes of study, have given insulin to similar patients. Knowing that the diabetes is inherently mild and that the reduction of a few pounds in weight would control it, one might expect that a small dose of insulin would suffice to accomplish the same result. *This is not so.* These patients are relatively resistant to insulin. Repeatedly over 100 units of insulin a day were necessary to accomplish in reducing the blood sugar level what was as readily obtained by a slight reduction in weight. These patients have three means to control their diabetes without insulin: viz., a low caloric diet, a reduction in weight, and physical exercise. All three are powerful agents in reducing the need for insulin. Various attempts have been made, especially by Himsworth,² to classify diabetic patients into insulin-resistant and insulin-sensitive groups. Most of the insulin-resistant patients were middle-aged or overweight. There seems to be a general lack of appreciation for

the fact that the overweight insulin resistant patient loses this resistance to insulin in direct proportion to the reduction of body weight. Any factor which reduces the total metabolism, with one exception (i.e., the cessation of physical exercise), aids in the control of the diabetes. Reduction in body mass seems to be the most effective of these factors. Newburgh has confirmed our work and extended the proof of benefit secured by reduction in weight in the obese diabetic patient.

The effect of a reduction in weight by virtue of a reduced caloric intake is illustrated in Table 22. One to several weeks are needed, as a rule, to control the diabetes in these overweight patients. All who are familiar with the effect of obesity on life expectancy agree that overweight should

TABLE 22

TYPICAL RESPONSE OF THE BLOOD SUGAR LEVEL AND GLYCOSURIA IN THE OBESE DIABETIC PATIENT TO THE RESTRICTION OF THE TOTAL CALORIC CONTENT OF THE DIET WITHOUT THE AID OF INSULIN

A Fe Female White Aged 51 Height 61 Inches Ideal Weight 135 Lbs 39 Per Cent Overweight

DATE	WEIGHT LBS	DIET			GLYCOSURIA	BLOOD SUGAR MG PER 100 CC
		P	C	CALORIES		
July 7 1933	188	70	80	1100	2 1%	250
July 21	181	70	80	1100	0	177
July 28	181½	70	80	1100	0	141
August 11	179	70	80	1100	0	122
October 20	170	70	95	1300	0	115
January 26 1934	167½	70	85	1200	0	110
August 24	153	70	95	1300	v ft trace	113
March 8 1935	148	70	105	1400	0	113
July 12	147	70	115	1600	0	110
October 9 1936	157½	70	115	1600	0	110
December 10	156	70	140	1600	0	120
June 25 1937	165	75	160	1800	0	113
August 13	161	75	160	1800	0	109

Summary With a loss of weight of 9 pounds the blood sugar level fell from 0.250 per cent to normal. Subsequently the carbohydrate tolerance was much improved. Even with an increase in weight of 14 pounds from the lowest level the blood sugar remained normal.

be corrected. In the diabetic this result, accomplished by appropriate dietary measures, carries a double benefit—it cures the obesity and controls the diabetes.

If, for any reason, the body weight is not reduced and the diabetes is not controlled, prolonged and needless hyperglycemia and glycosuria should not be allowed. Insulin should be employed. This is a recognition of failure, however. The patient will lose weight without insulin, as he should if he is convinced of the advantages that will accrue, and if he has the will power to resist excess food. Hospitalization, training and reassur-

ance are essential to the successful treatment in most of these problem cases

The obese patient's appetite is greater and a reduction in weight is more difficult to secure if he is given insulin. While insulin is harmless to such patients it misleads the patient into thinking that it is insulin, not the diet, that is important. Besides it is a wasteful practice.

C WHICH INSULIN*

There are five insulins commercially available—regular (or unmodified), crystalline,† protamine zinc insulin, globin and the recently released NPH insulin which is another modified insulin.

Protamine Zinc Insulin. This type of insulin is slowly absorbed and hence its blood-sugar lowering effect does not gain much headway in the first two or four hours after the injection (Fig. 3). The slow absorption of this insulin provides its greatest advantage—a prolonged effect. The blood sugar depressing effect of a dose of protamine zinc insulin lasts for twenty four to thirty six hours. In spite of the overlapping effect of the waning dose with that of the newly injected dose the combined effects are not adequate in most cases to prevent marked hyperglycemia and glycosuria during the forenoon.

It is always well to give the protamine zinc insulin in one dose daily one hour before breakfast unless combined with regular insulin.

Its greatest effect will be exerted during the daytime six to eighteen hours after injection when three meals come in close succession, and its diminishing effect will be exerted after midnight. It should be clear that the diminishing effect may in the absence of food during the long night period, be quite sufficient to provoke a hypoglycemia in the early morning. This is the time that a hypoglycemia due to protamine zinc insulin is most likely to occur. The larger the dose the more delayed is the maximum effect and the more likely are hypoglycemic reactions to occur in the early morning. A dose of 60 units of protamine zinc insulin was observed, in the course of a special study to have its greatest effect from twelve to twenty

* Crystalline insulin (zinc insulin crystals in solution) has an effect indistinguishable from that of regular insulin. The elimination of this insulin will reduce the confusion incident to the increasing number of insulins. Eli Lilly & Co. has stopped the commercial manufacturing of crystalline insulin.

† NPH insulin (Neutral Protamine Hagedorn) is a neutral crystalline protamine zinc insulin which acts more promptly in reducing the blood sugar than protamine zinc insulin—similar in this respect to globin insulin—and the blood-sugar lowering effect persists for at least twenty-four hours.

The advantages claimed for NPH insulin are: It is stable with little or no excess of protamine; regular insulin can be added to NPH insulin without much loss of its rapid blood-sugar lowering action; it fills the insulin need of a larger number of diabetic patients than is possible with protamine zinc insulin or globin insulin and the necessity of making insulin mixtures is somewhat reduced. There can be no doubt from our experience that this is a valuable insulin and when used in conjunction with suitable adjustments in diet and when necessary with added regular insulin it is superior to protamine zinc insulin for clinical practice.

hours after its injection, even though 20 grams of carbohydrate were given at two hour intervals throughout the period of observation (Fig 3) In clinical practice, the diminishing effect during the night is highly desirable, there being no food taken at this time Occasionally we hear of a dose of protamine zinc insulin being given before supper This practice would mean that the greatest intensity of the insulin action would be in operation during the early hours before breakfast and at a time when it is preferable to have the blood sugar lowering effect on the wage

A small dose of protamine zinc insulin may suffice to control the diabetes in relatively mild cases In the more severe cases when larger amounts of insulin (especially if more than 20 units) are needed, two features stand out (a) The slowness of insulin action permits the diabetes to get out of hand' in the forenoon, and (b) there is an increased risk of hypoglycemic reactions in the early morning These two features are corrected *first*, by the addition of a dose of regular insulin in the morning which acts promptly and tends to prevent the hyperglycemia and glycosuria in the forenoon, *second*, by a reduction of the dose of protamine zinc insulin, and *third*, by giving a bedtime nourishment, as indicated in the standard diets, pages 126 to 132

Protamine zinc insulin permits fewer injections of insulin, reduces the extent of oscillations of the blood sugar and controls the nocturnal blood sugar level It has reduced complications, notably ketosis, and many patients, who formerly would have had to weigh their food, do well using household measurements, because of protamine zinc insulin

From the practical standpoint protamine zinc insulin suffices to control the diabetes without supplementary regular insulin, in a very small percentage of patients, although the percentage successfully treated with this insulin alone can be extended by reducing the carbohydrate for breakfast and giving a bedtime nourishment

To determine the dose of protamine zinc insulin we follow *three* simple rules

(a) Part of the breakfast carbohydrate is given at bedtime

(b) Daily, or on alternate days, the insulin is increased, from a safe initial dose of approximately 12 units, by 4 to 12 units, depending on the degree of glycosuria * No further increases are made when the first urine voided before breakfast becomes free from sugar

(c) At this point two specimens of venous blood are taken for sugar

* During hospitalization complete fractional urine collections are made over specified periods namely 7 to 11 A M, 11 A M to 4 P M, 4 to 9 P M and 11 P M to 7 A M., and are examined for sugar At home suitable adjustments of the insulin dosage are made on the basis of tests made on single specimens of urine voided before each meal and at bedtime

It is often desirable for patients who rarely have glycosuria to test only the specimens most likely to contain sugar This information is presented in Table 23 according to the plan of insulin therapy employed.

determinations, one before breakfast and one two hours after lunch. If the fasting blood sugar value is below 120 mg per 100 cc, it is not safe, because of the danger of early morning hypoglycemic reactions, to increase the protamine zinc insulin, and if the post cibum blood sugar is below 160 mg per 100 cc and there is no sugar in the urine voided before each meal, we conclude that the diabetes is adequately controlled. In anticipation of a reduction in the need for insulin moderate reductions in dosage

TABLE 24

SATISFACTORY (A) AND UNSATISFACTORY (B) CONTROL OF THE DIABETES WITH ONE DOSE OF PROTAMINE ZINC INSULIN DAILY

PATIENT A						
Tests for Glycosuria						
Day of Treatment	Insulin PZI (Units)	9 P.M. - 7 A.M.	7-11 A.M.	11 A.M. - 4 P.M.	4-9 P.M.	Blood Sugar (mg per 100 cc)
4	None	++	++++	+++	+++	
5	8	++	+++	++	++	
6	8	+	++	++	++	
7	14	+	++	++	+	
8	14	0	+	0	+	
9	20	0	+	0	0	
10	20	0	0	0	0	Fasting 80 Post-cibum 130
PATIENT B						
6	40	0	++++	+++	+++	Fasting 66 3 P.M. 210

Indications for patient B: One dose of glit in insulin (see Table 25A) or a combination of protamine zinc and regular insulin (see Table 26)

are advisable after a few days of freedom from glycosuria. It will be noted in Tables 24 to 28, with the exception of the initial blood sugar determination, the degree of glycosuria is used as a guide to therapy until the urine becomes free from sugar, at which time pre- and post-cibum blood sugar determinations are done on the same day.

Fasting blood sugar values alone are a simple matter to determine. Fasting blood sugar values alone are not enough. Fasting blood sugar values alone should not be

adding. In fact, it is a normal with protamine zinc insulin blood sugar values determinations have

their place but, unfortunately, it is rather universal that they are the only blood sugar analyses done.

Usually, if the insulin need exceeds 20 units, one dose of protamine zinc insulin will not suffice for adequate control of the diabetes. In such cases the fasting blood sugar value may be below 120 mg and yet the two-hour post cibum value exceeds 200 mg as illustrated in Table 24 B, with glycosuria before lunch, supper and at bedtime. These are indications for an insulin which exerts a more prompt effect in the daytime and a shorter duration of action than occurs with protamine zinc insulin. Globin insulin

TABLE 25
GLOBIN INSULIN THERAPY SATISFACTORY (B) UNSATISFACTORY (C)

PATIENT B						
Tests for Glycosuria						
Day of Treatment	Insulin (units)	9 P.M. 7 A.M.	11 A.M.	11 A.M. 1 P.M.	4 P.M.	Blood Sugar (mg per 100 cc)
1	40 (PZI 1 hr act)	0	++++	+++	+++	Fasting 166 3 P.M. 230
2	10 (Globin 1 hr act)	0	++	0	+	
8	14	0	+	0	0	Fasting 121 3 P.M. 96
PATIENT C						
12	80 (Globin)	++	++++	0	0	Fasting 210 3 P.M. 80 (Hypoglycemia at 4.30 P.M.)

Indications for Patient C: One dose each of protamine zinc insulin and regular insulin given 15 minutes before breakfast (Table 26A).

fulfills these criteria and is the insulin of choice for those patients with diabetes of the next grade of greater severity (see Table 25). Or, a modest reduction of the protamine zinc insulin with a small dose of regular insulin injected separately, or, the same total amount given as a 2:1 mixture of regular and protamine zinc insulin, respectively, may be the next step.

Globin Insulin. A single dose of globin insulin given daily one hour before breakfast will control a considerably higher percentage of the cases of diabetes than is possible to do with a single daily dose of protamine zinc insulin. In fact, experience has shown that one dose of globin insulin daily can completely replace the single-dose therapy of protamine zinc in-

sulin and successfully extend its sphere of usefulness to the control of diabetes of a more severe grade

The speed with which globin insulin reduces the blood sugar increases as the dosage is increased. This effect is much more prominent than is the case with protamine zinc insulin (Fig 3)

For the patient for whom one dose of protamine zinc insulin is not adequate, as indicated above, globin insulin may suffice and by this means

TABLE 26

PROTAMINE ZINC INSULIN AND REGULAR INSULIN THERAPY (INJECTED SEPARATELY)
SATISFACTORY (C) UNSATISFACTORY (D)

PATIENT C						
Tests for Glycosuria						
Day of Treatment	Insulin	9 P M 7 A M	7-11 A M	11 A M- 4 P M	4 P M	Blood Sugar (mg per 100 cc)
12	80 Globin	++	++++	0	0	Fasting 210 3 P M 80
13	70 P Z I 12 Regular	++	+	+	+	
14	70 P Z I 12 Regular	0	0	+	+	Fasting 110 3 P M 110

A 2:1 mixture of the regular and protamine zinc insulins frequently gives satisfactory results e.g.

15	27 P Z I 54 Regular	0	0	+	0	
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PATIENT D

8	80 P Z I 24 Regular	0	0	++++	++++	Fasting 80 3 P M 270
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Indications for Patient D: One dose each of protamine zinc and globin insulin given 1 hour before breakfast (see Table 28D)

multiple doses or a mixture of insulin may be avoided. To determine the dosage of globin insulin the following rules (see Table 25) are recommended

(a) Ordinarily, only one dose of globin insulin is given daily and this is administered approximately one hour before breakfast. (Globin insulin is not given before supper, except in rare cases and then in small amounts. If this timing of administration is employed it is important to realize that the most intensive insulin action from a pre supper dose occurs during the night.)

(b) A portion, usually one milk and one carbohydrate exchange, is taken from the breakfast and is given to the patient between 3 and 4 P.M. daily as a means of reducing the likelihood of a hypoglycemia before supper when the apparent effect of globin insulin is greatest. Additions of 4 or 8 units on alternate days to the initial dose of 8 to 16 units are made until the specimen of urine voided before supper is free from sugar. At this point 3 P.M. and fasting venous blood sugar values are determined. If the patient is free from hypoglycemic reactions, if the 3 P.M. blood sugar is between 80 and 130 mg per cc., and if the fasting blood sugar does not exceed 130 mg per 100 cc. the diabetes is under satisfactory control. Moderate reductions in the dose of insulin are advisable after a few days of good control of the diabetes and a further decrease is usual when normal activities are resumed. Further minor adjustments are made as indications arise. The steps taken in arriving at the dosage of globin insulin as well as the detection of the cases in which it is not satisfactory are illustrated in Table 26. Some patients prefer globin insulin solely because there is practically no danger of a hypoglycemia during the night as exists with protamine zinc insulin. We have delineated the sphere in which globin insulin is most valuable. In this sphere it has in our experience yielded better results than other preparations or mixtures of insulin. Globin insulin is almost universally satisfactory for patients not requiring more than 40 units daily and when the proper adjustment of the diet is observed. In a decreasing percentage satisfactory results are secured with doses in excess of 40 units. However one of our patients takes a single dose of 86 units of globin insulin with good results. Like the other insulins globin insulin has its realm of best activity and we suspect that it is because the criteria used in arriving at the proper dosage are different from those for the other insulins that failures have resulted. Globin insulin has a secure place in the treatment for diabetes until a better insulin than is available at present is discovered.

If the 3 P.M. blood sugar value referred to above is between 80 and 130 mg per 100 cc. and the fasting blood sugar is in excess of 200 mg with early morning glycosuria and glycosuria before lunch it is clear that further increases in the dose of globin insulin should not be made, because of the danger of hypoglycemia in the late afternoon, and yet, the diabetes is not well controlled. Ordinarily we abandon globin in preference to a combination of regular and protamine zinc insulins under these circumstances.

Insulin Combinations: Protamine Zinc Globin and Regular Insulin and Mixtures. An injection each of protamine zinc insulin and regular insulin is given one-half hour before breakfast when the rapid action of regular insulin and the prolonged action of protamine zinc insulin are needed. The initial doses will vary but for purpose of illustration, 20 units of protamine zinc insulin and 6 units of regular insulin are injected

separately. The urine voided before each meal and at bedtime is tested for sugar. Daily increases of 2, or 4, or 6 units may be added to the regular insulin until the specimen before lunch becomes free from sugar. Similarly, the protamine zinc insulin is increased until the first specimen voided in the morning is free from sugar. At this point samples of blood for sugar determination are taken before each meal and at 9 P.M. This four test curve secured when circumstances warrant is of much greater value than single daily tests. If all values are satisfactory—between 80 and 150 mg

TABLE 27

PROTAMINE ZINC AND GLOBIN INSULIN THERAPY (INJECTED SEPARATELY)
SATISFACTORY (D) UNSATISFACTORY (E)

PATIENT D						
Tests for Glycosuria						
Day of Treatment	Insulin	9 P.M.—7 A.M.	7 H.A.M.	11 A.M.—4 P.M.	4 P.M.	Blood Sugar (mg per 100 cc)
8	80 P.Z.I. 24 Regular	0	0	++++	++++	Fasting 80 3 P.M. 270
9	70 P.Z.I. 34 Globin	0	+++	0	+	
10	70 P.Z.I. 34 Globin	0	++	0	+	Fasting 130 3 P.M. 100

To avoid 2 injections a mixture of regular and P.Z.I. insulins may be tried 21—the results meet our standards in only 10 to 20 per cent of cases.

PATIENT E

8	80 P.Z.I. 32 Globin	0	++++	0	+++	Fasting 84 11 A.M. 280 3 P.M. 60 9 P.M. 230
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Indications for Patient E: A dose each of protamine zinc and regular insulin injected separately 15 minutes to ½ hour before breakfast and a small dose of regular insulin before supper (see Table 28).

per 100 cc—no further change is made, as in the case illustration in Table 26C. In the more severe cases at 9 P.M. hyperglycemia may remain as the only unsatisfactory blood sugar value and there is also a 4 plus reaction for glycosuria on testing the 9 P.M. specimen. Several methods are available to cope with this circumstance. First, combined globin and protamine zinc insulin therapy (injected separately), illustrated in Table 27D, will correct the evening hyperglycemia and if given one hour before breakfast, a forenoon hyperglycemia may be prevented. When successful only two injections are needed. When this combination is used a milk and a

carbohydrate exchange is taken from the breakfast and given between 3 and 4 P. M. to insure against a hypoglycemia before supper due to globin insulin, and a milk and a carbohydrate exchange, deducted from the evening meal, are taken at bedtime, as illustrated in Figure 19, to guard against the risk of a hypoglycemia in the early morning hours due to protamine

TABLE 28

PROTAMINE ZINC AND REGULAR INSULIN BEFORE BREAKFAST AND REGULAR INSULIN BEFORE SUPPER TO CONTROL A SEVERE DIABETES

PATIENT P						
Tests for Glycosuria						
Day of Treatment	Insulin	9 P. M. 7 A. M.	7-11 A. M.	11 A. M. 4 P. M.	4-9 P. M.	Blood Sugar (mg per 100 cc.)
8	80 P. Z. I. 32 Globin	0	++++	0	+++	Fasting 84 11 A. M. 280 3 P. M. 60 9 P. M. 230
9	80 P. Z. I. 12 Regular before breakfast 10 Regular before supper	0	++	+++	0	
10	74 P. Z. I. 18 Regular before breakfast 10 Regular before supper	0	0	++	0	Fasting 124 11 A. M. 140 3 P. M. 169 9 P. M. 110

One or the other of two alternative plans might be tried to avoid the three injections.

(a) A mixture of regular and protamine zinc insulin 2:1 (occasionally 3:1)—initial dose being 68 units of regular and 34 units of protamine zinc insulin mixed and injected simultaneously from the one syringe.

or
(b) A mixture (1:1) of NPH and regular insulins—the initial dose being 80 units of NPH and 20 units of regular insulin.

zinc insulin. These adjustments in diet are not found to be inconvenient. Patients like them. They increase the patient's safety and they permit larger amounts of insulin to be given and better control of the diabetes results.

In a second, or alternative plan, the protamine zinc insulin and regular

insulin given before breakfast are supplemented by a small dose of regular insulin before supper and adjusted until results are satisfactory (see Table 28). Injections of combined regular and protamine zinc insulin are properly given about fifteen minutes before breakfast. If given longer before the meal the likelihood of hypoglycemic reactions is greater before breakfast, owing to the rapid action of regular insulin at the time in the twenty-four hours when the blood sugar is usually lowest because of the retarded action of the protamine zinc insulin. Because of the rapid action of regular insulin the full quota of food, one third of the total diet, after deducting a milk and bread exchange, is given for breakfast. The one milk and one bread exchange are given at bedtime as a safety measure against a hypoglycemia in the early morning (Fig. 17). The patient may take a portion of his lunch at 11 A.M. to increase the margin of safety against a hypoglycemia before lunch time. Usually this measure is not necessary. *Third* the total number of units found to control the diabetes by the two injections before breakfast and one before supper are given in a single injection as a 1:1 mixture* of regular and protamine zinc insulin or, rarely, a 3:1 mixture is more effective. To guard against hypoglycemic reactions the same measures are taken as when two injections are given before breakfast and one before supper, presented above.

Insulin mixtures are, at times, surprisingly satisfactory in controlling severe grades of diabetes. This is the exception, however. Not more than 20 per cent of our patients do as well as we want them to on the mixture therapy. However, we believe that to avoid multiple doses the mixture method should be tried and if good results are not obtained separate injections are recommended.

Regular Insulin. There is an occasional patient who, because of allergic manifestations, is unable to use protamine zinc insulin. In this event globin insulin, to which allergic responses are rarely, if ever, seen, may be tried. In the event that neither of these insulins is tolerated recourse may be had to the use of regular insulin as it was employed in the pre-Hagedorn era.

Examination of the fractional collections of urine for sugar already indicated is used as a guide in increasing the insulin until the urine is free from or contains only a trace of sugar.

One dose, 8 to 12 units, of regular insulin given twenty minutes before breakfast may suffice to control a relatively mild diabetes. Usually more is necessary. While sugar continues to appear in the 7 to 11 A.M. specimens

* Protamine zinc insulin contains sufficient excess protamine to combine with added regular insulin up to approximately a 1:1 mixture.² Hence if a rapid effect is expected from regular insulin added to protamine zinc insulin the ratio must be greater than 1:1. A ratio of 2:1 is the most widely effective mixture but a ratio of 3 of regular to 1 of protamine zinc insulin is used occasionally. The results from mixtures of globin and regular insulin are in our experience, too unpredictable for clinical practice.

2 to 8 units may be added daily. When the dose reaches 18 or 20 units or if the 7 to 11 A.M. urine becomes free from sugar while the other fractions contain sugar, it is well to give *two doses*. These may be given as follows: 12 units twenty minutes before breakfast and 6 units before supper. It is well to make no increase in the total dose at the time it is divided. The mere splitting of the dose has the same effect as an increase. The smaller the dose of regular insulin, the more effective is each unit.

Further increases, 2 to 4 units daily, are made to the morning dose while glycosuria persists in the 7 to 11 A.M. urine fraction, and to the evening dose while there is sugar in the 1 to 9 P.M. fraction.

Three doses are usually indicated when the amounts have reached the neighborhood of 20-0-16. The division might be as follows: 16 units before breakfast, 8 units before lunch and 12 units before supper, prescribed as 16-8-12. Small additions, 2 to 4 units, may be made daily as outlined above. Glycosuria in the 11 A.M. to 4 P.M. collection indicates an increase in the noon dose while freedom from glycosuria would suggest no change. This applies also to the other doses and specimens. An occasional patient does better with a small third dose given at bedtime instead of before lunch.

The foregoing plan of treatment serves the majority of these patients who require insulin. There is, however, a group of more severe cases in which a point is reached when, if additions are made to any one of the three doses of insulin, a hypoglycemia results during the day and yet a hyperglycemia occurs in the early morning. This is due to three large doses fairly close together on one hand and a long night period without insulin on the other. The diabetes is so severe that when the effect of the evening insulin is exhausted and the patient has not enough endogenous insulin to keep the blood sugar at a normal level during the remainder of the night, a progressive increase in the blood sugar concentration occurs. This accounts for the morning hyperglycemia despite the normal blood sugar values throughout the remainder of the day. Allen¹ suggested lengthening the day periods between doses and shortening the night period without insulin by giving the morning insulin one hour earlier. The timing of the noon dose remains unchanged but the evening dose is given one or two hours after supper. When the severity of the diabetes calls for this plan, there need be no fear of a hypoglycemia during the night. A portion of the supper may be taken at bedtime if a safeguard seems necessary.

When a fourth dose is necessary, as occasionally occurs in patients having severe diabetes, it is well to give it at midnight, with a small amount of nourishment (1 milk and 1 bread exchange). The other three doses, in event of the fourth dose being needed, should be given prior to the respective meals. The fourth dose is usually needed for a short period only.

The great fields of usefulness for *regular insulin* are (1) in combination with protamine zinc insulin and with NPH insulin therapies, and (2) in the treatment during acute complications of diabetes (Chapter VII).

II ADMINISTRATION OF INSULIN

There is no feature in the treatment of diabetes that necessitates more detailed instruction than that of insulin administration. In order that no important aspects be missed the instruction is dealt with under the following captions:

- | | |
|--------------------------------|------------------------------|
| 1 Commercial brands of insulin | 5 Site of injection |
| 2 Preservation of insulin | 6 Withdrawal of insulin |
| 3 Syringe and needle | 7 Technic of mixing insulins |
| 4 Sterilization of equipment | 8 Timing of injection |

1 Commercial Brands of Insulin. There are four different insulins in widespread use:

- Regular insulin *
- Globin insulin
- Protamine zinc insulin
- NPH insulin

Each insulin is available commercially in two strengths:

- U 40 red label 40 units per cc
- U 80 green label 80 units per cc

Patients are trained to avoid confusion and error in measuring insulin by *always* using a syringe showing graduations up to 40 units per cc when U 40 insulin is being used and a syringe showing graduations to 80 units per cc in the case of U 80 insulin. Serious errors of dosage—some times a double dose and other times one half a dose—are traceable to confusion resulting from measuring U 40 insulin on U 80 calibrations or vice versa. Although accurate measuring is possible by this method it fosters confusion, errors and inaccurate recordings.

Patients are taught that a unit of U 40 insulin has exactly the same effect as a unit of U 80 and that the reason for two different concentrations is that they allow, for patients taking large doses of insulin, the injection of twice as many units, by taking U 80 insulin instead of U 40, without increasing the volume of fluid injected.

■ Preservation of Insulin. Commercial insulins are remarkably stable. A bottle of insulin being drawn from daily does not need to be refrigerated. It does not deteriorate at room temperature even if the daily withdrawals are small. Also, the injection of insulin at room temperature causes less discomfort and, in some cases, less local reaction, and greatly reduces, or possibly eliminates, the likelihood of subcutaneous fat atrophy with disfiguring pitting of the skin. We have had patients live in the tropics and use insulin at current atmospheric temperatures with no bad effect. Refrigeration is desirable for reserve supplies of insulin and bottles from which some insulin has been withdrawn but which are not in

* Zinc insulin crystals in solution—crystalline insulin—is available but as its action is for practical purposes identical with that of regular insulin² and as its production has been greatly curtailed it is needless to deal with this insulin separately.

daily use. Freezing of insulin should be provided against, as it reduces its potency.

3 Syringe and Needle. The official insulin syringes* adopted by the American Diabetes Association* are available in three models

- 1 A 1 cc syringe with calibrations for U 40 insulin with markings in red enamel—total capacity 10 units
- 2 A 1 cc syringe with calibrations for U 80 insulin with markings in green enamel—total capacity 80 units, and
- 3 A 2 cc syringe calibrated for U 80 insulin with markings in green enamel total capacity 160 units

The markings in red and green enamel conform with the colors of the labels on the bottles of U 40 and U 80 insulins, respectively. Confusion and mishaps will be reduced if these standard syringes are used exclusively for the administration of insulin.

Needles $\frac{1}{2}$ inch in length with 25 gauge and made of rustless steel, are to be preferred. They are less likely to be broken and when the needle is thrust through the skin at right angles there is less risk of injecting the insulin intramuscularly than if longer needles are used. If longer needles are preferred, injection at an angle of 45 degrees is advisable.

4 Sterilization of Equipment. Alcohol sterilization of syringe and needle suffices provided they are not used to give injections to any but the one patient. Alcohol does not destroy certain viruses, notably the hepatitis virus. Outbreaks of hepatitis have occurred in diabetic clinics^{1, 2} in which the sterilization of syringes was inadequate. Alcohol sterilization of syringe and needle has been employed in some clinics in which the morning dose of insulin is administered by the nurse to the patient after the withdrawal of a sample of blood for testing. If needles and syringes are to be used for more than one individual, sterilization should be by autoclaving, or by boiling for a minimum of fifteen minutes.

The patient's personal equipment for insulin injection is organized on a tray or in a suitable container. It comprises: insulin, one bottle of alcohol—ordinary commercial rubbing alcohol is satisfactory—cotton, insulin syringe, and two needles. A stone—an Arkansas oil stone—upon which to sharpen needles is a useful adjunct.

5 Site of Injection. Insulin is administered *subcutaneously*—not intramuscularly or intravenously (except as noted on p. 231). When the patient makes the injection himself which is practically always the case except in very small children and during complications, the thighs and abdomen are the most convenient sites. Some can also use the arms—over the deltoid muscles. Subcutaneous injections by nurses are usually made into the deltoid and buttock regions. The site should be varied in a manner that will prevent an injection in the same spot more than once in two

* These syringes may be secured locally or from Becton Dickinson Company, Rutherford, N. J.

weeks. Injections should not be made into indurated areas or in close proximity to depressions due to decrease in subcutaneous fat.

6 Withdrawal of Insulin. A small ball of cotton is soaked with alcohol and used to thoroughly cleanse the rubber cap on the insulin bottle. The pledget of cotton is then allowed to rest on top of the insulin bottle until the syringe and needle are prepared. The needle is adjusted on the syringe and, with the full length of the needle immersed in alcohol, the plunger is withdrawn until the syringe is full of alcohol. The alcohol is expelled into the bottle and air is drawn in and expelled repeatedly from the syringe until the needle and syringe are dry.

Regular and globin insulins do not need to be agitated but protamine zinc insulin which tends to settle in the bottom of the bottle is uniformly suspended by rolling the bottle between one's hands. It should not be shaken, as this causes bubble formation and interferes with making a homogeneous distribution of the insulin which is contained in the milky particles.

The next motion is to insert the needle through the cork into the insulin bottle and expel an amount of air, equal to or in excess of the dose of insulin to be withdrawn, into the bottle. The insulin bottle is held in the inverted and vertical position and insulin is allowed to flow into the syringe. This occurs without pulling on the plunger if the proper degree of positive pressure exists in the bottle. A bubble or two may enter the syringe. These are expelled into the bottle and the exact amount of insulin needed is measured and the needle is withdrawn from the bottle.

The site for injection, having been selected, is thoroughly rubbed with the alcohol soaked pledget and the needle ($1\frac{1}{2}$ inch) is plunged full length and vertically through the skin. After slight traction on the plunger reveals that the needle is not in a blood vessel the contents are discharged. The needle is withdrawn and the area rubbed again with the alcohol soaked pledget. If blood enters the syringe the needle is withdrawn half its length before discharging the insulin.

The syringe is rinsed free of insulin by drawing alcohol into and discharging from the syringe several times. The bottle of alcohol should be stoppered at all times except when in use. Alcohol evaporates readily when exposed to the air, leaving water with no antiseptic properties.

7 Technic of Mixing Insulins. The technic is modified when a mixture of insulins is used. Both insulin bottletops are cleansed with the bottles standing upright and an amount of air equivalent to or in excess of the dose of the respective insulin to be withdrawn is injected into each bottle. The air is injected into the bottle of protamine zinc insulin first—but no insulin is withdrawn—and then into the bottle containing regular insulin which is then inverted and the appropriate amount of insulin withdrawn. Regular insulin is always withdrawn first—a measure which prevents the introduction of even minute quantities of protamine zinc insulin into the bottle of regular insulin. The syringe is held in the vertical position with

the needle pointing upward. The bottle of regular insulin is removed and the bottle of protamine zinc insulin is then substituted from which is drawn the proper amount of insulin.

By holding the syringe upright throughout this maneuver the two insulins will, for practical purposes, remain unmixed in the syringe and if some bubbles must be returned to the protamine zinc insulin bottle this can be done without discharging any of the underlying regular insulin into the bottle containing the protamine zinc insulin. Also, by maintaining positive pressure in each bottle, as directed, it will not be necessary to cope with the difficulty presented by a multitude of small bubbles in the syringe brought about when insulin is withdrawn against a negative pressure—the bubbles entering along the barrel of the syringe when the plunger is forcibly withdrawn. With the proper amounts of each insulin in the syringe, the bottle of protamine zinc insulin is removed from the needle and the syringe is inverted several times in order to mix the insulins, which are then injected.

8 Timing of the Injection of Insulin.* The time relationship between the injection of insulin and the taking of food depends largely on the type of insulin used (see Table 23). When protamine zinc only, or globin only, or a dose each of protamine zinc and globin insulin is used, the injection is given one hour before breakfast. A mixture of regular and protamine zinc is injected about fifteen minutes, or immediately, before breakfast. Regular insulin when employed to the exclusion of the slower acting insulins in the treatment for acute complications is injected just before meals (see p. 215). The timing of the injection of regular insulin in the rare case of intolerance to the slowly acting insulins and in the absence of complications depends on the severity of the diabetes as to whether it is injected fifteen minutes before the taking of food or one hour before breakfast, just before lunch and one hour after supper or at bedtime. This aspect is dealt with on page 146. Many injections of regular insulin, as given in the treatment for diabetic coma in the initial stages, have no relation to food or glucose administration (see p. 231).

COMPLICATIONS OF INSULIN THERAPY

(Hypoglycemia Allergic reaction Fat dystrophy Insulin edema
Presbyopia Social problems)

Hypoglycemia (Insulin Reaction)†

Cause and Nature of Hypoglycemic Reactions in Diabetes. A hypoglycemic reaction occurs when too much insulin has been given in

* A single dose of NPH insulin is administered one hour before breakfast but if regular insulin has been added to NPH insulin the mixture is injected fifteen minutes or just before breakfast daily.

† "Hypoglycemic reactions" or "insulin reactions" are the acceptable terms and are preferable to "insulin shock" which is misleading. It is not until the patient is in extremis that it can truly be said that he is in shock. The signs and symptoms of a hypoglycemic reaction as usually observed are as of shock.

relation to food intake, physical exercise, decreasing resistance to insulin as complications subside, and to improving carbohydrate tolerance in the absence of complications. The usual amount of insulin may prove to be excessive (a) if only a part of a meal is eaten, (b) if with the diet and insulin constant there is an unusual increase in physical exercise, (c) if appropriate reductions are not made in the insulin dosage as an acute infection subsides, (d) when the carbohydrate tolerance improves with the control of the diabetes, (e) if there is faulty distribution of the diet, or (f) if there is improper timing of the administration of insulin. These are common causes of hypoglycemic reactions associated with insulin therapy but all features which tend to reduce the need for insulin predispose to hypoglycemic reactions. The less common are included in Table 29.

TABLE 29

CAUSES—FUNDAMENTAL AND PREDISPOSING—OF HYPOGLYCEMIAS DUE TO INSULIN THERAPY

A Fundamental

- 1 Too much insulin
- 2 Too little food

B Predisposing

- 1 Increased exercise
- 2 Faulty distribution of diet and vomiting
- 3 Improper timing of insulin injections
- 4 Improved tolerance as
 - a Diabetes is controlled
 - b Complicating ketosis infection or toxemia subsides
 - c Body weight is reduced
 - d Pregnancy is terminated
- 5 Undernutrition
- 6 Change in the site of insulin injection from an insulin tumefaction to other areas
- 7 Correction of thyrotoxicosis

An insulin reaction is characterized by a depression of the venous blood sugar level below normal—usually below 60 mg per 100 cc. Values down to zero have been recorded.

The onset of symptoms characteristic of a hypoglycemia commences at a higher blood sugar level when the hypoglycemia is due to regular insulin than when it is caused by protamine zinc insulin. The slowness of the action of the latter, presumably, permits better adjustment to the falling blood sugar concentration, hence when symptoms do occur they indicate a greater depletion of the blood sugar than is the case when the reduction is brought about more rapidly. As a result it is not uncommon to find venous blood sugar values as low as 55 or 60 mg per 100 cc., or even lower, without symptoms in the case of an overdose of protamine zinc insulin. Ordinarily, this is not the case if these values are due to regular insulin.

Physical Exertion Physical exertion in all but severe and untreated diabetes, has a blood sugar lowering effect. This feature assumes special

importance in the patients taking large doses of insulin. An adjusted sedentary regimen interrupted by a game of golf, tennis, hiking or other strenuous exercise is very likely to be complicated by a hypoglycemic reaction unless more food than usual has been ingested or unless a moderate reduction in the previous dose of insulin has been made. The insulin need tends to be less, for many patients, in the summer time when increased exercise is the rule.

Faulty Distribution of the Diet The failure to have the patient using globin insulin take a 3 to 4 p.m. nourishment predisposes to hypoglycemic reactions before supper. The omission of bedtime nourishment by the patient taking protamine zinc insulin increases the likelihood of an insulin reaction before breakfast (see Table 23). Delayed or reduced meals are predisposing causes of insulin reactions. If the patient is taking regular insulin before breakfast a reduced breakfast and a delayed lunch would operate in favor of an insulin reaction as would a reduced luncheon and delayed supper in the case of globin insulin therapy, and a reduced supper and omission or reduction of the bedtime nourishment in the case of protamine zinc insulin therapy. Vomiting of food after insulin has been given leaves the patient exposed to a possible insulin reaction if the diabetes is controlled and if precautionary measures are not taken. Small liquid feedings may be permitted at one-hour intervals until glycosuria is noted or if oral feeding is contraindicated glucose, a 5 per cent solution in distilled water, may be administered slowly by vein.

Improper Timing of Insulin Injection Patients taking both protamine zinc insulin and regular insulin before breakfast are more liable to have an insulin reaction if the insulin is given too long before breakfast. Injection immediately before or not more than fifteen minutes before breakfast reduces this risk to a minimum. We never give two daily doses of protamine zinc insulin, but if one dose is given before breakfast and a second is given before supper the danger of an early morning hypoglycemia is intensified. In some instances we give a small dose of globin insulin before supper in addition to the larger maintaining dose before breakfast. This practice, unless rigidly controlled predisposes to insulin reactions in the early morning.

Overdosage of insulin, through error in measurement is an uncommon cause of hypoglycemia. When it does occur it is usually associated with one of the following: (a) insulin administered by some one not fully trained in the technique, (b) measuring insulin of one strength (U 100) in a syringe graduated for another (U 40), (c) errors in making mixtures of insulin, e.g. an erroneous reversal of a 2 U mixture of regular and protamine zinc insulin would intensify the protamine zinc insulin action and predispose to a hypoglycemia in the early morning.

Improved Tolerance for Carbohydrate The initial control of the diabetes with insulin is followed by a reduced insulin need in most cases. This

improvement may be measured in terms of a few to many units. Failing to anticipate this improvement by reducing the insulin, as control of the hyperglycemia is achieved, makes insulin reactions probable. This gain in tolerance is noted in uncomplicated diabetes but it is much more marked when complications, notably infections, ketosis and toxemias, are brought under control. The reduced insulin need may be measured in hundreds of units, and when suitable reductions are made insulin reactions are unlikely.

Undernutrition Patients who receive insulin and at the same time are on a weight reducing regimen may develop insulin reactions as their weight decreases. Reduction of body weight has a profound influence in reducing the need for insulin. This is true of a reduction as a planned therapy but it also occurs in cases of malnutrition accompanying debilitating diseases such as malignant disorders and occasionally with the emaciation that occurs with tuberculosis.

The *termination of pregnancy* in most cases is accompanied by an increased sensitivity to insulin. As in the correction of obesity, the termination of pregnancy reduces the total metabolism and predisposition to hypoglycemic reactions is increased as a result.

Changing Site of Insulin Injection Insulin may be relatively ineffective when injected into indurated areas or into insulin tumefactions but hypoglycemic reactions may be precipitated without changing the dose but by injecting the insulin into loose subcutaneous tissues.

Symptoms of Hypoglycemia The symptoms characterizing varying degrees of severity of hypoglycemic reactions are as follows:

Mild Reaction Mild hypoglycemic reactions exhibit symptoms of a stimulated sympathetic nervous system: hunger, weakness, tremulousness, nervous instability, mild emotional disturbances, headache, mild mental confusion and depression, and a detached manner in answering questions.

Reaction of Moderate Severity As the more severe grades of hypoglycemia develop disturbances in the central nervous system and psychiatric manifestations occur—increased weakness, excessive perspiration with skin cold and clammy to the touch, numbness of tongue, lips or buccal mucosa, cardiac palpitation, difficulty in mental concentration, loss of memory, diplopia, staring expression, blurring of vision, difficulty in walking, impaired coordination, increased emotional instability and disorientation.

Severe hypoglycemic reactions include twitching of muscles, convulsions, unconsciousness, paraplegias, incontinence of urine and, in unusual cases, transient hemiplegia. Protracted coma for hours or days even after the blood sugar is restored to normal may rarely occur. Mental deterioration is a rare complication of prolonged severe hypoglycemic states. Fatalities due to insulin reactions are rare. They are most likely to occur in debilitated individuals with poor glycogen

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served in the early stages. They occur most frequently between midnight and breakfast time. The patient may be found stuporous or in an unconscious state drenched with perspiration. He may on the other hand feel weak on rising and have a cloud over his mind until he has eaten. Headache is particularly common during an interval following the correction of a hypoglycemia due to profane neglect of insulin. Altered retrograde amnesia is common. Patients may go about their duties in a dazed manner for varying periods before attracting attention or before taking food and yet they may have no recollection of driving home, of crossing the street, of the conclusion of an important meeting or other happenings many of which carry the possibility of grave danger to the imprudent.

Illustrative Cases. J. H., aged 47 years, after a long room and proceeded to his home coming to a man thoroughly concerned. I was no longer there. He was doing his work. Her food has an unusual sensation was suspected. Upon recovery the patient has no recollection of taking his last room of finding his way home. The patient is now a college graduate and teaching school.

Patien E. M., an insurance salesman, had no recollection of what occurred in a two-hour period during which he drove his automobile unaccompanied for 18 miles along a busy highway around traffic. He ended by running into a post. He was found near a field by six cooper who on finding his automobile dent location. A full bottle of orange juice a supply of which they found in his automobile. The possible ending of the accident is many. This experience was the result of an attempt on the part of a careless patient to balance a break in the restraint with an error of loss of insulin.

Diagnosis. A history indicating that the patient has diabetes and a recent insulin treatment is helpful. This information is not always obtainable and even if it is the possibility of unconsciousness resulting from other causes makes a careful differential diagnosis important.

The patient in an insulin reaction may exhibit a range from slight transient moments of confusion to complete unconsciousness. The mode and time of onset of symptoms are important. The patient may appear "queer," a fixed expression is common and conversation may be without proper sequence. He may behave like an automaton. He appears confused and is emotionally upset over trivial matters or without apparent cause. He may become hysterical and resist examination and treatment. The onset of unconsciousness before mealtime should make one suspect hypoglycemia while if it occurs between one and three hours after a hearty meal hypoglycemia is less likely to be the cause.

There is usually some pallor of the skin but in general the patient's appearance is not that of a person who has been ill but that of one who has fasted. The skin is wet. Beads of perspiration are common on the forehead at the hair margin, the face, body and extremities are cold and clammy and the underclothes are wet with perspiration. The body temperature may be slightly below normal. The pupils are dilated, the intraocular tension is not disturbed, the pulse rate is advanced with normal or increased force and the blood pressure is either normal or as frequently

occurs, is elevated. It falls below normal only when the patient is in *extremis*. The breathing is undisturbed. Marks from the injection of insulin are usually apparent on legs, arms or abdomen. The tendon reflexes are overactive and a Babinski sign may be elicited during but not immediately after recovery from the reaction.

The examination of the urine offers little of value in confirming the diagnosis. The absence of glycosuria is suggestive evidence, however, in the case of an unconscious patient known to have diabetes and known to take insulin. Furthermore the absence of glycosuria and ketonuria is definite evidence against diabetic ketosis. On the other hand, the patient whose blood sugar goes quickly from a high to a low level may have sugar in the bladder urine from a preceding hyperglycemic phase. Sugar in the first specimen obtained from the unconscious patient should not rule out the possibility of a hypoglycemia. After the bladder has been emptied, a second specimen should contain no sugar in case of a hypoglycemia.

A low blood sugar level, below 60 mg. per 100 cc., is the most important single evidence of an insulin reaction. One must make a diagnosis on clinical evidence, however, and begin treatment. The patient's welfare should not be jeopardized by delaying therapy until the blood sugar concentration is known.

Differential Diagnosis. The most frequent causes of unconsciousness likely to be confused with insulin reactions are alcoholism, diabetic coma (ketosis) and intracranial lesions. Trauma, poisonings, epilepsy, uremia, syphilis of the central nervous system, and rarely, hyperinsulinism, malaria and Addison's disease may simulate, in part, a hypoglycemia due to an overdose of insulin. Night sweats of tuberculous infections complicating diabetes are occasionally suggestive of, and may be confused with an insulin reaction.

Diabetic Coma (Ketosis). The chief characteristics of diabetic coma are presented on page 226 and the characteristic clinical differences between diabetic coma and an insulin reaction are presented in Table 30. In contrast to the patient having an insulin reaction, the patient in coma (ketosis) has received too little insulin, there is marked *dehydration and air hunger* (Kussmaul breathing) with an *odor of acetone on the breath*, the onset of symptoms is slow, at least eight to twelve hours, and is preceded by *anorexia, thirst, polyuria* and later *vomiting*, the pulse is weak and rapid and the blood pressure is subnormal, the *tendon reflexes* are diminished and the plantar reflexes are normal, there is usually no twitching of the muscles or convulsions, glycosuria and acetoneuria are present, there is often a complicating infection in the ketotic patient and finally the blood sugar level is above normal, the plasma acetone is promptly detectable (see p. 227) and the carbon dioxide combining power of the blood plasma is reduced.

If there is any doubt whether one is dealing with diabetic coma (ketosis)

or an insulin reaction (hypoglycemia), the therapeutic test of giving glucose (dextrose), 20 cc of a 50 per cent solution in distilled water, intravenously, should be made. This will do the ketotic patient no harm and it will restore the hypoglycemic individual to consciousness in most cases.

Intracranial Lesions. The more common intracranial lesions that are likely to confuse one in making the diagnosis are hemorrhage, thrombosis

TABLE 30

A COMPARISON OF THE CLINICAL EXHIBITS OF HYPOLYCEMIA AND DIABETIC COMA (KETOSIS)

	HYPOLYCEMIA	DIABETIC COMA (KETOSIS)
Cause	Too much insulin or not enough food	Not enough insulin
General appearance	A well person who has fainted	Very ill
Breathing	Normal	Rapid and deep (air hunger)
Onset	Rapid (minutes)	Slow at least 12 hours
Hunger	Great	Absent
Thirst	None	Great
Vomiting	Rare	Common
Eyes	Staring and pupils dilated	Normal
Disturbed vision	Diplopia and difficulty in focusing	Hazy
Headache	Common	Absent
Intraocular tension	Normal	Increased
Skin	Wet (especially face and neck)	Dry
Thirst	Normal	Dehydrated
Pulse	Full and rapid	Weak and rapid
Air hunger	Absent	Present
Blood pressure	Increased or normal	Slightly normal
Cardiac palpitation	Frequent	Absent
Constipation	None	Present
Muscular twitching	Common	Absent
Nervousness	Common	Absent
Babinski's sign	Common	Absent
Complicating infections	Absent	Common
Abdominal pain	Absent	Common
Urine sugar	None after residual urine is discarded	Present
Blood sugar	Below normal	Above normal
Acetonuria	Absent	Present
Response to treatment	Rapid (minutes)	Slow (hours)

and emboli in cerebral vessels, tumors and trauma. A careful physical examination will reveal signs of arterial disease, localizing neurologic signs or evidence of trauma and there will be no marks of the insulin injection. The blood sugar level will be normal or moderately elevated and glycosuria is common when there is injury to the base of the brain. This response is due to stimulation of the sympathetic centers.

Treatment of Hypoglycemia. The hypoglycemia should be corrected without delay. Mild reactions are readily remedied by having the patient

drink a glassful (240 cc) of orange juice, or take four or six glucose lozenges (8 or 12 gm). All patients taking insulin should carry these lozenges or lumps of sugar with them. Any sweets will serve the same purpose. Cane sugar must be reduced to a monosaccharide before it is absorbed, hence is somewhat slower than glucose in correcting a hypoglycemia. Honey, molasses, syrup and hard candy are all effective but if not available other carbohydrate foods may be given if the patient is able to take food by mouth. Fruits, cereals, bread or crackers will correct mild reactions. Often it is only necessary to take a meal a trifle earlier than usual and make suitable changes in the insulin dosage on the following day.

There is danger in feeding an unconscious patient. Atelectasis and pneumonia may result from the inhalation of food into the lungs during this procedure. If there is no alternative the risk is reduced if the patient is held in a sitting position and fed slowly with a spoon. Liquids should not be poured into the mouth of an unconscious patient. One or two glucose lozenges or, lacking these, a lump of sugar placed between the cheeks and teeth will dissolve slowly and be swallowed with little risk.

Dextrose 20 cc of a 50 per cent solution in distilled water is given intravenously without delay to the patient who is unconscious or having convulsions as a result of a hypoglycemia. The recovery from unconsciousness is prompt. Often consciousness is restored before the intravenous injection is completed. Should this measure fail to restore consciousness a continuous intravenous administration of a 10 per cent solution of glucose (dextrose) in distilled water is begun. This latter measure is rarely necessary but in instances in which enormous doses of insulin are taken by mistake it may be life saving. Consciousness having been restored intravenous treatment is no longer necessary, but when the reaction is due to protamine zinc insulin it is a good plan to give 10 or 20 gm of carbohydrate half hourly or hourly until the next meal is taken or until glycosuria is provoked. In this manner one can prevent hypoglycemic reactions due to protamine zinc insulin which are apt to recur because of the continued action of insulin after their temporary correction. A recurrence of the reaction is not likely when the hypoglycemia follows overdosage with regular insulin.

If sterile glucose is unobtainable and if feedings by mouth are not practical, carbohydrate in liquid form may be administered via a tube passed through one nasal passage and into the stomach. The withdrawal of fluid which turns blue litmus red is proof that the tube is in the stomach and not in a bronchus. This precautionary test should always be made. Retention of food in the stomach may prevent absorption of carbohydrate hence too much reliance should not be placed on oral or tube feedings if there is not a prompt (within ten or fifteen minutes), satisfactory clinical response.

The hypoglycemic individual absorbs considerable glucose if it is administered by rectum. Twenty grams of glucose or corn syrup dissolved

in 6 ounces of warm water and given by the Murphy drip or intermittent methods have served well in emergencies on several occasions when instructions regarding treatment had to be given to the patient's relatives by long-distance communication.

Epinephrine (adrenalin), 0.5 to 1.0 cc of a 1 in 1000 solution given subcutaneously, may cause a return of consciousness and allow food to be taken by mouth. It operates by liberating glucose from glycogen. Little effect can be expected from epinephrine in the emaciated patient or in the patient who has a severe reaction from protamine zinc insulin in which the hepatic glycogen is heavily drawn upon before symptoms of a hypoglycemia appear. Epinephrine is effective in the well nourished patient and when the hypoglycemia is the result of an overdose of a rapidly acting insulin. The effect of the epinephrine in any case is only transitory. It should never be relied upon alone but should be supported by the administration of food.

Diabetic Identification Card Every diabetic patient taking insulin should carry an appropriate identification card. Such a card doubtless saved the lives of at least two of our patients and saved one patient from a sojourn in a prison cell. The cards employed at the Pennsylvania Hospital carry the following information:

I HAVE DIABETES AND TAKE INSULIN

If I am found ill, unconscious or behaving unnaturally

Place a candy or lump of sugar between my cheeks and teeth or feed me orange juice slowly

If not improved in 15 minutes

take or send me to a hospital or notify my physician

My name is

Address

Telephone

My physician is

Address

Telephone

Prevention of Insulin Reactions (Hypoglycemia). A recurrence of an insulin reaction may be prevented by reducing the insulin on the day following a reaction and on succeeding days. If the reaction occurs before breakfast the protamine zinc insulin should be reduced by 2 to 8 units, if it occurs before lunch the morning dose of regular insulin is responsible and should be reduced by 2 to 8 units thereafter, if the reaction occurs in the late evening the dose of insulin given before supper should be reduced by a similar amount.

It is not wise to reduce the insulin dosage without determining the cause of the reaction. Should the hypoglycemia have followed unusual exercise,

an omitted meal or vomiting, no reduction is indicated on the following day if normal conditions are restored

Insulin reactions may be prevented in the following ways

1 A small reduction of the insulin dosage, of 4 to 12 units, is made when unusual and strenuous exercise is planned. When the usual amount of insulin has been injected and extra exercise is taken a moderate addition to the usual diet, such as a banana, a glass of milk or a glass of orange juice, is advisable. A regular daily plan of exercise, uniform in time and amount, will reduce the likelihood of reactions.

2 In event of vomiting the amount of insulin is reduced to one-half the usual requirement if there is no glycosuria, keeping in mind that even if food is not ingested metabolism of the body tissues continues. Rarely indeed should a dose be completely omitted, though this is a common (and dangerous) practice. Each specimen of urine is examined separately and if heavy glycosuria should occur more insulin is given. This plan is also adopted in case of diarrhea. Close supervision of the diabetic patient who is vomiting or has diarrhea is essential, as in one patient they may cause hypoglycemic reactions and in another ketosis. In case of vomiting, food by mouth should be stopped. Nourishment in the form of a 10 per cent solution of glucose (dextrose) may be given by vein, one liter every eight hours. At least one liter of normal saline is indicated in each twenty-four hours, as are amino acid preparations, in protracted cases. Regular insulin is given at six-hour intervals (p. 220). In case of diarrhea, bland foods and those which tend to cause constipation are allowed although intra-venous therapy may be needed in severe cases.

3 Appropriate reductions are made in the insulin dosage after the diabetes is brought under control. A gain in carbohydrate and total food tolerance occurs at this time and the need for insulin decreases proportionately. A decrease of 4 to 8 units a day until glycosuria occurs is a good practice. At this point a small increase in the amount of insulin given will usually suffice to adequately control the diabetes. Greater reductions should follow the reduction in body weight and eradication of ketosis, infections and toxemia.

4 Increasing the insulin too rapidly is a cause of reactions which is easily avoided. The increases in the amount of insulin given should be small—2 or 4 units daily—as control of the diabetes is approached.

5 The timing and distribution of the insulin are arranged according to the plan presented on page 141. It is especially important, when a rapidly acting insulin and protamine zinc insulin are given before breakfast, that the meal be not delayed more than fifteen minutes after the insulins are administered. The same is true of the evening meal if a dose of regular insulin is given before the meal. This precaution is necessary because of the presence of a combined action of protamine zinc insulin and regular insulin at the end of a considerable period without food.

6 The likelihood that reactions will occur before lunch is reduced, in the patient susceptible to reactions, by taking part of the lunch—the fruit or milk—at 10:30 or 11 A.M. Similarly the likelihood of early morning hypoglycemic reactions is greatly reduced by taking food at bedtime (see p. 140). When globin insulin is employed, a milk and a bread exchange, deducted from the breakfast, and taken at 3 P.M., aids in preventing late afternoon reactions.

7. A small reduction—4 to 12 units—of the insulin dosage when the patient is discharged from the hospital is a wise precaution to offset the effect which the increased exercise has in precipitating low blood sugar levels.

Allergic Reactions to Insulin

Local reactions about the site of the insulin injection, believed to be allergic, are manifested by swelling, redness, discomfort and itching. They are common when protamine zinc insulin is used and unusual when the rapidly acting insulins or globin insulin are given. Swollen and indurated areas about an inch or an inch and a half in diameter appear and become hot and tender. These local reactions first appear from two to twelve hours after the injection is given. The reaction is at its height from eighteen to twenty-four hours, after which the inflammatory reaction and the swelling gradually subside until there is no trace of them in three or four days. In the sensitive patient, there may be three or four of these "areas" in the various stages of progression and regression at one time. Fortunately within three or four weeks desensitization usually occurs spontaneously.

It is rare to encounter a patient allergic to insulin protein itself, identified by noting allergic reactions to all forms of insulin. Allergic sensitivity to the specific animal protein is somewhat more frequent and is identified, as an example, when relief follows the change from insulin of pork origin to that made from beef.* The most common of all allergic manifestations to insulin therapy are associated with sensitivity to protamine zinc insulin—associated spontaneously in most cases and in the persistent cases, by changing to globin insulin. The addition of protamine—having no antigenic properties—to insulin, a true antigen—is believed to create a higher incidence of sensitivity to insulin than when insulin alone is injected into individuals having no detectable sensitivity to protamine solution (Horn and Langner).† Resumption of insulin therapy after a lapse of weeks to years is followed in a week to ten days by systemic reactions: urticaria, swelling of face and extremities in some patients having an allergic sensitivity to insulin.

By recrystallizing mixed beef and pork insulin several times Jorgensen

* Insulin available commercially is of pork and beef (cattle) origin with the exception of the Sharp & Bohme product which is of beef origin. Beef insulin is available on request from Eli Lilly & Company. Recrystallized insulin is not commercially available in this country as yet.

was successful in retaining the activity of the insulin while eliminating impurities which were considered to be the causes of the allergic reactions

It is rare to find a patient allergic to globin insulin but if sensitivity to the insulin protein is present—an uncommon occurrence—it is to be expected that allergic response will follow the injection of insulin of any brand or source

Treatment for Allergic Reactions to Insulin. 1 It may be practicable to omit insulin. This is always the case in the obese patient with uncomplicated diabetes. Control of the diabetes by appropriate restriction in diet and reduction in weight will avoid untoward allergic reactions from insulin. It must be assumed, however, that every diabetic patient will sooner or later develop acute complications and will need insulin temporarily. It is therefore of great importance to clearly establish his allergic status and determine which insulin, if any, he can take without risk of severe allergic reactions. If he has an allergic sensitivity to all insulins desensitization is recommended, after which insulin is given with sufficient frequency to avoid a return of his sensitivity. In the case of the obese diabetic one injection per week will suffice, whereas daily injections will be needed for therapy in the thin diabetics.

2 No special treatment is needed for the common local reactions which subside spontaneously after a few weeks of continued insulin therapy.

3 Allergic reactions to protamine zinc insulin of sufficient severity to warrant more vigorous action usually subside by changing from protamine zinc insulin to globin insulin. Changing of the commercial brand of insulin—from one lot of insulin to another or from the product of one pharmaceutical company to that of another—has been beneficial on some occasions. This is attributable in most cases to changing the animal source of insulin.

Generalized urticaria or constitutional reactions, especially edema of the face and mucous membranes, dyspnea, prostration, gastro-intestinal symptoms and stiffness of joints following insulin administration are uncommon but present a genuine problem when they occur.

These reactions as well as the persistence of severe local reactions are treated as follows:

a Epinephrine hydrochloride (adrenalin) 1:1000, subcutaneously, 0.5 cc for an adult and 0.2 cc for a child. The dose is repeated as frequently as every half hour depending upon the severity of the reaction. In extreme emergencies epinephrine may be given intravenously but at a very slow rate and in doses of 0.3 to 0.5 cc.

b Ephedrine sulfate is given by mouth 25 mg ($\frac{3}{8}$ gr) for the adult and 8 mg ($\frac{1}{8}$ gr) for the child, at four hour intervals until improvement occurs.

c One of the antihistamine drugs is given orally at four hour intervals until relief is secured and maintained.

Rapid desensitization is indicated when the reaction to each of the available insulins is severe in a person who must have insulin. The patient may have a severe infection or be in a state of pre-coma, or coma. In either case desensitization to allergic reactions to insulin may be life saving. We have given subcutaneous injections of minute quantities of regular insulin at ten to twenty minute intervals. Increases are made from the initial dose of $\frac{1}{1000}$ of a unit to $\frac{1}{500}$ to $\frac{1}{250}$ and so on, doubling the dose for each successive injection until it reaches 1 unit. If no significant local reaction develops when this amount is given, therapeutic amounts are administered to control the diabetes. In this program of desensitization the anticipated increase is delayed and the same dose repeated in the event that an untoward local reaction develops. The desensitization to regular insulin is recommended because it is this brand of insulin that is used in the event of acute complications. It is important that no interruption in insulin therapy be permitted following desensitization, in this manner reducing to a minimum the return of hypersensitivity to insulin.

Illustrative Case Report R. G., male, aged sixty-five years, with onset of diabetes in October 1939 took insulin from January until March, 1940. In August 1940 insulin was resumed because of a small carbuncle. After nine days the patient developed urticaria and his face began to swell especially his lower lip and under his eyes. He was found by intracutaneous tests, to be sensitive to all available (seven) brands of insulin. He was rapidly and successfully desensitized with regular insulin beginning with $\frac{1}{500}$ of a unit in distilled water and doubling the dose at ten minute intervals except when a definite wheal formed in which event no increase was made when the next injection was given. This program was continued until within three hours, it was possible to give 1 unit subcutaneously. A dose of 5 units was then given subcutaneously without ill effect.

Fat Dystrophies

Insulin Tumefactions. Local painless, indurated areas of fat hypertrophy sometimes occur where insulin is injected in the same area over long periods. The swelling is "sulbery" to palpation and the skin is adherent to the subcutaneous tissue. Not infrequently the overlying skin is peculiarly insensitive to pain. For this reason patients, especially children, wish to have the insulin injected into this area, but as the induration interferes with absorption of the insulin, this is a bad practice.

Treatment consists of changing the site of injection in such a manner that one site will not be used a second time in any fortnight. The swelling gradually subsides. Injections of insulin elsewhere with a more rapid absorption may precipitate hypoglycemic reactions unless suitable adjustments in the dosage are made.

Fat Atrophy Due to Insulin. Concave depressions in the cutaneous contour due to atrophy of subcutaneous fat and appearing in areas into which insulin has been injected over relatively long periods—several weeks to several years—are not uncommon in child diabetics of both sexes and of adult females—usually under thirty years of age (Fig. 20). The combi-

tion is not common in the adult male diabetic population. Fat atrophy in areas remote from the injected area has been reported.

The cause of the fat atrophy at the site of the insulin injection is unknown beyond the fact that it is related to insulin therapy. Many theories have been put forward in explanation of its cause—faulty technic of administration of insulin, impurities in the alcohol used for cleansing and sterilizing purposes, the preservative in insulin, local metabolic reactions, the low temperature of insulin when injected, local injury and androgen insufficiency. The sex and age occurrence suggests that the androgens may



Fig. 20 Fat Atrophy. Concave pitting of the skin due to atrophy of fat in locations used for injecting refrigerated insulin (Patient J H). This disfigurement disappeared in three months when insulin at room temperature was used and without changing the site of injection.

have a protective effect against this disorder. On the other hand, the paucity of subcutaneous fat in the adult male may be a factor. The condition is not restricted to insulin therapy, as repeated injections of pituitrin in the treatment for diabetes insipidus are known to have caused it. Varying of the sites of the injection has been recommended as a preventive measure. In our experience no local lipodystrophy has occurred as long as the insulin injected is at room temperature. In fact, this simple measure has led to the correction of the deformity without altering the site of injections.

This disfiguring but harmless condition is corrected by varying the sites of injection of insulin in such a manner that a site will not be used for injection twice in any fortnight. The injection of insulin which has been

allowed to reach room temperature is the most effective preventive measure. The pitting disappears slowly, requiring from two to four months and rarely one to two years to subside completely.

Insulin Edema

A filling-out of the face, giving it a waxy appearance, smooth and free from wrinkling with a reduction of facial expression, is seen in some patients following the rapid control of a severe diabetes with insulin. An imbalance in the osmotic pressure between circulatory and tissue fluids caused by withdrawal of glucose from the blood is believed to be responsible. These patients are usually, but not always, young females. One patient had not only the "insulin facies" but extensive edema of his extremities and disturbance of vision as well during the first few weeks he received insulin. This patient had a complicating xanthoma diabeticorum with a blood cholesterol of 1666 mg per 100 cc and a severe diabetes. The water retention probably was exaggerated by the high carbohydrate diet which was allowed.

Ordinarily no special treatment is necessary for this "insulin edema" though in the case referred to above the edema was so extensive that the salt was withdrawn from the patient's diet and for a few days he was given ammonium chloride, 13 gm (grains 20), three times daily. It is well to investigate the kidney function of any diabetic who has demonstrable edema, which is one of the outstanding signs of an intercapillary glomerulonephritis (Kimmelstiel Wilson's disease) (see p. 197).

Presbyopia Due to Insulin

A transient presbyopia occurs in a considerable number of patients when they receive insulin for the first time. This disturbance is attributed to a reduced elasticity of the lens and is probably the consequence of a disturbance of the adjusted osmotic pressure in the tissue of the lens and circulating fluids. The result is difficulty in focusing vision on nearby objects. The changes are bilateral. The degree of change usually amounts to about 2 diopters but in the young patients, in whom the condition is most troublesome, changes of 4 diopters are sometimes observed. This disturbing complication has occurred in my experience for the most part in young adult patients, whereas Wilder states: "This disturbance in vision is much more marked in individuals who are approaching the age of natural presbyopia and whose lenses, because of age, have already lost elasticity."

This disturbance is entirely apart from hypoglycemic reactions and fortunately after two to four weeks of treatment the presbyopia precipitated by insulin therapy, disappears entirely.

The patient should be advised that the disturbance is temporary. Glasses purchased at such a time, though satisfactory during the period of presbyopia, would gradually become unsuitable with the restoration of the

normal osmotic equilibrium between the lens and ocular fluids. Examinations preparatory to prescribing for glasses should be delayed until at least six weeks have elapsed subsequent to control of the diabetes. The temporary derangement will have disappeared by this time. In isolated instances it may be desirable to overcome this disturbance in vision from the beginning of treatment by securing suitable lenses for temporary use.

Insulin Therapy as a Social Problem

All child diabetics need insulin and special consideration of their diets. These factors tend to make them different from normal children. Children resent "being different" more than do adults. The adjustment problem is a great one. It will require sympathetic understanding on the part of the doctor if the young patient's confidence is obtained to a degree which makes it more satisfying to the patient to heed his advice and derive the full benefits of treatment than it is to "follow the crowd." This is a real test for the doctor. It is a real test for the patient. This feature is dealt with in more detail in Chapter XIV.

Diabetic patients have a higher than average intellect, yet if it is known by a prospective employer that the candidate for a position has diabetes and uses insulin, the chances of employment are reduced if not eliminated. The increasing number of diabetic patients intensifies this problem on a national and international scale.

The diabetic who has a hypoglycemic reaction in public is suspected of being intoxicated. If, by chance, he has the odor of alcohol on his breath during a hypoglycemic reaction, he may be subjected to the indignities attending arrest and to the danger of his unidentified hypoglycemia while awaiting a hearing. One patient, because of his behavior in a restaurant where he sought relief from a hypoglycemic reaction, was considered to be drunk and was thrown out bodily. The encounter with a police officer which followed, ended happily when the patient produced a diabetic identification card.

Diabetic patients taking more than 20 units of insulin daily should not engage in occupations that expose them to power driven machinery or that entail the driving of an automobile. The patient taking large amounts of insulin, who drives a private automobile, is cautioned that he should take extra food before doing so, especially if he does so just before meal time.

The social problem which diabetes presents is a big one, and one of many varieties, concerning all ages, occupations and all walks of life. In the treatment of diabetic patients a high degree of individualization is the rule. The aims should be (a) to control the diabetes adequately without making the program so inflexible, or so exacting that to follow it can hardly be expected, (b) to adopt effective safeguards against hypoglycemic reactions—to maintain a high standard of health in general and to under

stand the individual's social problem and guide him in such a manner that in doing what gives him greatest satisfaction he will include the measures best suited to cope with his diabetes and his social adjustment.

Insulin Resistance of Marked Degree

Barring acute complications of diabetes severe degrees of idiopathic resistance to insulin are uncommon and their cause is unknown. One of our patients (J.G.) had an insulin need in 1917 which altered in a rhythmic fashion between 100 and 2500 units daily for many months. The only apparent complicating factor was a cholelithiasis with no acute manifestations. No abrupt change followed the cholecystectomy but over several months which followed, the need for insulin decreased gradually and when last seen in August, 1950, her diabetes was controlled by 176 units daily.

Great increases in the resistance to insulin are common during (a) *acute complications*, notably infections, ketosis, acute disseminated pancreatitis, and uncommonly during acute parenchymal disease of the liver, and (b) *chronic complications*, especially the following: allergic manifestations, disease of the adrenal and pituitary glands and hemochromatosis.

Unknown Disorders. It is the insulin resistance that elevates the daily need to extremely large doses—many hundreds of units—without any apparent cause that is the mystery. These cases are rare in contrast to the common occurrence of insulin resistance, in excess of 200 units daily, occurring during acute complications.

Causes of Insulin Resistance. When due to acute complications the insulin resistance rapidly subsides with control and correction of the precipitating condition, whereas insulin resistance due to undetectable causes tends to subside spontaneously but gradually over periods of months or years. There is an occasional exception to this rule. Sinclo¹¹ reports a patient who required 700 to 800 units daily five and one half years after the onset of the insulin resistance. Our patient (J.G.) takes 176 units after three and one half years.

In view of the fact that the underlying disturbance in the physiology of these chronic cases, without obvious complication, is entirely speculative a review of the subject here is not considered appropriate. It suffices to place our suspicion on aberrations in the cellular enzyme systems. Hormonal disturbances are known to increase the need for insulin but it is doubtful if this explains such cases as that referred to above, in which on careful evaluation no such disturbance was detected.

It has been suggested that the insulin is excreted in the urine. If so, it is not in an active form, as the injection into a mouse of appreciable quantities of such a patient's urine after a huge injection of insulin has no hypoglycemic effect.

Treatment of Insulin Resistance. 1. Acute complications are dealt with as outlined in Chapter XVI.

2 Insulin is given in sufficient amounts and with sufficient frequency to avoid ketosis. When no cause is detected it may be necessary to treat these patients identically as one would treat them for an acute complication. It was necessary, in the case of J. G., to give regular insulin in doses as high as 475 units every four hours day and night over a prolonged period. Attempts to give fewer doses or smaller amounts resulted in the prompt appearance of ketosis. The ultimate favorable outcome, as illustrated by this case, is the rule.

INSTRUCTION OF THE PATIENT

Patients will benefit from a general knowledge of diabetes. They will find a regular source of information written especially for them in *The Forecast*,* a bimonthly publication. Patients untutored in this subject are likely to abandon treatment and believe themselves cured. All who treat diabetic patients have seen those who come for help because of failing vision, or peripheral vascular disease, or degenerative disease of the kidneys and who give a history of diabetes of which they believed themselves cured years previously. We are not certain that diabetes is ever cured and in any case, if it is, the infrequency of this occurrence is such as to make it of no practicable importance except to that rare individual who is involved. We hold out no hope of a cure from means now at hand but do try to dispel the fears that many patients have, fears born of a background of all the worst cases they have occasion to remember. We owe it to these worried patients promptly to point out the comparison of the outlook for diabetic patients in the present with that of the pre-insulin era.

A few days are spent in the hospital for the purpose of controlling the diabetes and instructing the patient. However, this is but an introduction to a lifetime study and training. The instruction deals with

- 1 General knowledge of diabetes
- 2 Causes of the symptoms of diabetes
 - Hunger
 - Thirst
 - Loss of weight
 - Polyuria
 - Weakness
- 3 Sugar in the urine
 - Source and amount
 - Relation to blood sugar
 - Tests for sugar in the urine
 - What urine specimens to test
 - Is sugar in the urine always an indication of diabetes?
- 4 The blood sugar
 - Normal values
 - Why blood sugar determinations are necessary
 - Range of blood sugar values in untreated diabetes and in controlled diabetes
- 5 Diet prescription
 - Protein fat carbohydrate and total calories

* Published by the American Diabetes Association, Inc. 11 West 42nd St. New York 18, N. Y.

- Diet menu from diet prescription
- Selection and preparation of foods
- Measuring of foods
- Weighing of foods—rarely necessary
- Distribution of diet
- 7 Exercise
 - Effect on patient's weight
 - Effect on blood sugar
 - Effect on need for insulin
 - Adjustment of diet and insulin needs because of exercise
- 8 Insulin
 - Need for insulin and dosage
 - Commercial brands and their identification
 - Administration
 - Sterilization and maintenance of equipment
 - Measurement and mixing when indicated
 - Site of injection
 - Timing of injection
- 9 Insulin reactions (Hypoglycemia)
 - Definition
 - Symptoms
 - Treatment
 - Cause and prevention
 - Times that reactions are most likely to occur
- 10 Changes in body weight and diabetes
 - Loss of weight in treatment for diabetes
 - Loss of weight in untreated diabetic patient
 - Gain in weight
- 11 What to do in case of unretained food—vomiting or diarrhea and in case of complete loss of appetite with aversion to food
- 12 Infections and diabetes
 - Sugar in urine
 - Blood sugar
 - Ketosis (coma)
 - What to do in case of infection
- 13 Diabetic coma (ketosis)
 - Definition
 - Causes
 - Prevention
 - What to do if ketosis is suspected
- 14 Care of the feet
- 15 Surgery and diabetes
- 16 Misbeliefs—especially about the outlook, insulin substitutes, there are none—and insulin addiction

This training of the diabetic patient will carry over for weeks and months but before discharge from the hospital the patient should clearly understand

- 1 The preparation, measuring or weighing in case this is necessary, and the distribution of the diet
- 2 The kind or brands of insulin he is receiving, the dose he should take, the time of the injection and how and where to administer the insulin
- 3 The symptoms of an insulin reaction and how to correct them
- 4 How to test the urine for sugar and to know which specimen should be tested

5 How to keep an up to date record indicating dates, diet, insulin dosage and results of the tests for sugar in the urine

Exercise. Physical exercise, judiciously employed by patients who have no contraindicating conditions, is of inestimable value in the treatment for diabetes. It improves the total food and carbohydrate tolerance and reduces the need for insulin. In the overweight patient having a mild diabetes exercise has two beneficial effects, (a) an insulin like action in reducing the blood sugar level and (b) the reduction of body weight which reduces the need for insulin. Hence, the patient quickly learns that glycosuria tends to occur when he is physically inactive and that it subsides when he is active.

In untreated undernourished patients having severe diabetes exercise is not helpful but actually accentuates the wasting processes characteristic of this disease and the blood sugar level is increased instead of lowered. But, exercise becomes a helpful instead of a harmful agent in these cases when the diabetes is adequately treated with diet and insulin. Its blood sugar lowering effect is restored and all the advantages that accrue as the result of a good physical condition are added. The decrease in the need for insulin following discharge from the hospital is largely due to the effect of exercise, an effect which is anticipated by a modest reduction in the insulin.

Exercise as an instrument of therapy is best used by having the patient remain relatively active during the initial period of hospitalization—by making active exercise a daily routine and one of uniform extent and regularity of time as far as practicability will permit. An ordinary amount of exercise should never be curtailed in the well treated diabetic unless some complication dictates otherwise. Exercise producing undue fatigue is undesirable, however. It will not always be possible to regulate the amount of exercise from day to day, hence the importance of teaching patients that increased exercise will have an effect similar to added insulin and that omission of exercise will have the opposite effect. They are instructed that exercise during that time of day when they are most likely to have hypoglycemic reactions (see Table 23) will increase this risk. Meals following increased exercise should not be delayed. A reduction in the amount of insulin given prior to increased exercise is frequently advised. Patients learn from experience what reduction serves best to prevent an insulin reaction on one hand or glycosuria on the other. The dose that is to be reduced will depend upon the time of day that the extra exercise is taken. For instance, the patient who takes protamine zinc insulin and regular insulin before breakfast and who elects to play tennis before lunch reduces the regular insulin by 6 to 12 units and does not delay his luncheon. If on the other hand he or she spends the evening roller skating or dancing the reduction should be from the protamine zinc insulin and the bedtime nourishment might be increased but under no circumstances omitted. The pa-

patient taking a dose each of protamine zinc insulin and globin insulin before breakfast and who plans to undertake extra exercise during the afternoon may safely reduce the globin insulin, the amount being judged by experience according to the amount of exercise. Extra food at lunch and/or an increased 3 P.M. nourishment would reduce the need for a smaller dose of insulin.

In the case of a severe diabetes requiring a dose of regular insulin before supper, as well as regular and protamine zinc insulins before breakfast, the reduction is from the dose of insulin taken before supper in the event of extra exercise in the evening.

Adjustments counteracting the hypoglycemic effects of extra exercise are best made by increased food intake for patients taking insulin mixtures, as the mixtures do not lend themselves to as accurate predictions as when the insulins are injected separately. In these cases it is a good practice to take an apple, or an extra glass of milk and 5 soda crackers, or a banana at the meal preceding the exercise, or this nourishment can be taken advantageously just before or, less favorably, during the exercise, and the meal subsequent to the exercise should not be delayed.

Profound hypoglycemic reactions are likely if these measures are ignored by patients taking large amounts of insulin.

Care of the Skin. With good control of the diabetes these patients are no more subject to disorders of the skin than are nondiabetic individuals. Emphasis is, however, given to the need for good hygiene—plenty of soap and water daily and meticulous attention to the cleanliness of underclothing. The male subject is advised against having barbers shave the back of his neck because it is believed that this practice increases the incidence of furunculosis and of carbuncles. Two patients seen recently had carbuncles—one on the back of the neck and one on the scalp. Each was due to *Staphylococcus aureus* organisms which were completely resistant to penicillin—clinically and by laboratory testing. Though the antibiotic therapies have proved of immense value in coping with these complications we still consider them among the serious dangers to the diabetic.

Care of the Teeth. Thorough cleansing of the teeth with an ammoniated dental powder after each meal and at bedtime will go far in counteracting the predisposition which diabetic patients have to the development of dental cavities and gingivitis. Proper nutrition is also important in this respect. A dental survey, every six months, is recommended.

Care of the Feet. The impoverishment of the circulation in the feet of diabetic patients who are past middle age is so common that special care of the feet is necessary to prevent complications, particularly gangrene. In addition to the control of the diabetes preventive measures include

- A. Foot hygiene
- B. Avoidance of injury
- C. Callus formation and corns—correction and prevention

D Epidermophytosis—prevention and treatment

E Special measures

A Foot Hygiene 1 Take a warm (never hot) foot bath each evening. Dry feet gently but thoroughly and especially between the toes with a soft absorbent towel.

2 Anoint the feet with toilet lanolin after bathing, once to three times weekly, sufficient to keep the skin soft. Substitute rubbing alcohol for the lanolin if the skin becomes too soft.

3 Cut the toenails straight across even with the ends of the toes—never short and never cut back at the sides.

4 Once weekly the feet should be powdered—with talcum or if there is a predilection to epidermophytosis a film of fungicidal foot powder is rubbed in gently and some is carefully dispersed between the toes. The treatment for epidermophytosis is discussed on page 194.

B Avoid injury to the toes and feet 1 Exercise care in cutting the nails.

2 Wear comfortably fitting shoes made of soft leather.

3 Never place the foot on the floor except in a shoe or slipper.

4 Use care in the treatment for corns and calluses.

5 Never apply hot water bottles, heating pads or other external heating appliances to the feet.

■ Avoid irritating medicaments to the feet, especially iodine, phenol and proprietary preparations for removing corns and calluses.

7 Prevent and correct epidermophytosis.

8 Avoid hose with raised seams.

9 Break in new shoes very gradually—one hour daily at first.

Corrective measures dealing with (C) Calluses and Corns (D) Epidermophytosis and (E) Special Measures—Buerger's exercises, passive vascular exercise, ligation of veins and the immersion of hands and arms in hot water—for improving circulation of the feet will be dealt with in the prevention of gangrene, page 189.

Cautioning of Patients Against Unsubstantiated Claims. Patients with diabetes are prone to scrutinize news releases on medical subjects in the hope for some advance in the treatment for diabetes. Patients are cautioned against premature conclusions—sometimes on the part of the original author but usually on the part of the press. Also, claims made by manufacturers of proprietary products often lack substantiation. In one instance honey was expounded as having curative value for the diabetic. Special brews of one kind or another crop up from time to time for which great claims are made but which to date have not benefited diabetic subjects.

Patients may need to be reminded that they have an adequate diet and with insulin the diabetes can be controlled even under the most adverse circumstances. With sufficient concrete measures on hand they can afford to wait for the coming of new and better chances, one of these.

turns out as one might hope for nothing has been lost. Furthermore, dangers, false hopes, expense and disappointments will have been avoided.

The great desire for a remedy that will be effective when taken orally is easily understood. However, as yet *there is no substitute for insulin and insulin is not effective when taken by mouth.*

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CHAPTER XV

Complications of Diabetes

INTRODUCTION

Chronic complications, notably degenerative disturbances of the vascular and nervous systems and of the kidneys, present problems of a nature quite different from those of acute complications. They cause no appreciable change in the severity of the diabetes. The real problem is that these chronic complications are common and that once established they tend to progress, and it is they, and not the diabetes per se, that incapacitate and threaten life. The measures recommended in dealing with these chronic degenerative disorders pertain to good control of the diabetes month after month and year after year, to suitable changes in diet, and to preventive and corrective procedures that may be indicated in the individual case. These features are dealt with under their respective headings elsewhere in this chapter.

Nondegenerative disorders of a chronic nature which complicate diabetes are, in general, treated as in the nondiabetic with appropriate adjustments to insure adequate control of the diabetes.

Every diabetic patient will have an *acute complication* sooner or later. Whether it is an acute appendicitis, tonsillitis, carbuncle or other acute disturbance, the treatment that is satisfactory under usual conditions abruptly becomes inadequate. The blood sugar increases in concentration above normal and large amounts of sugar are lost in the urine. The anorexia so common during acute febrile episodes may lead the uninformed to omit insulin at such times. This mistake may lead to grave dangers.

Too much emphasis cannot be put on, *first*, the unfavorable effect which most acute complications have on the diabetes. Even the patient who ordinarily does not need insulin may suddenly—within a matter of hours—present the indications for emergency insulin therapy. A good illustration of this is the obese diabetic patient, E. H., a synopsis of whose case record is presented on page 236. This patient with a mild diabetes developed diabetic coma during an acute infection and was in a perilous condition requiring 1750 units of insulin in the first twenty-four hours of treatment. The *second* feature of acute complications is also illustrated by this case, namely, that as the acute complication subsides the severity of the diabetes

is reduced and, in this case, satisfactory control of the disorder was maintained without insulin. *Thirdly*, good control of the diabetes is an important aid in overcoming the acute complication and it makes complete return to the pre-complication status of the diabetes more certain than if the diabetes is allowed to remain out of hand during the acute episode. *Fourthly*, the ease with which even the most severe case of diabetes can be controlled during these trying periods is to be emphasized.

It is not true that the diabetes cannot be controlled during acute complications. It is not true that poor control of the diabetes does not alter the outlook in an unfavorable manner. It is not true that diabetic patients are unfavorable risks nor that they respond less well than nondiabetic patients to sulfa or antihypertensive therapy. Recognizing these principles, the physician who is familiar with the need to alter the diet and its distribution and to adjust the insulin therapy, as the indications for these changes will arise, will tide the diabetic patient through acute crises with very little, if any, more risk than if the patient were not diabetic.

An illustrative case is presented on page 209, depicting the methods of therapy employed at the Pennsylvania Hospital. Separate sections are devoted to the problems presented by other complications of an acute nature, notably pregnancy, infections, surgical conditions and diabetic coma.

CHRONIC COMPLICATIONS

1 Degenerative Vascular Lesions

Three distinct abnormalities, usually grouped under the heading of arteriosclerosis, are especially common in the diabetic population and appear at an earlier age than in nondiabetics. These are (a) *atherosclerosis*—essentially a disease of the intima; (b) *calcification of the arterial walls* (Monckeberg's sclerosis); and (c) *arteriolar sclerosis*. All grades of involvement from minimal to extensive changes of an advanced nature are seen. These three subcategories of arteriosclerosis are apparently independent of each other; any one may occur singly or they may be combined in the same patient. However, whatever underlying processes are at work, all three are commonly associated with diabetes and especially diabetes that has not been well treated and is of long duration. These changes are apt to appear at an early age—in the twenties—and far outstrip in progressiveness similar changes seen in older nondiabetic individuals. The early start, the speed with which the degenerative processes progress, and the advanced degree of the degenerative changes in the diabetic patient are in contrast with the later onset, the slow progress, and the lesser degree of the same disorder in nondiabetic individuals.

The incidence of advanced and incapacitating arterial disease is increasing at an alarming rate. This increase is attributed to the prolonged

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The incidence of advanced and incapacitating arterial disease is increasing at an alarming rate. This increase is attributed to the prolonged

life span of the diabetic. The average life span in the Naunyn era was 44.5 and in the Best era, 61.5 years.¹ This is undoubtedly part of the answer but other factors associated with diabetes are at work, factors which so far, have defied unraveling. It is into this field that most intensive research activities should be directed. A basis upon which to appraise improvement or other change, will be established if a most careful evaluation of the arteriosclerotic status, in its broadest aspects, is made in every case. This will involve especially a most careful history dealing with symptoms and functional capacity, *retinoscopy*, *blood pressure determinations*, notation of the *degree of thickening of the palpable arteries*, the *extent of the cardiac borders*, preferably determined by fluoroscopy and recorded by roentgen ray pictures, *electrocardiogram*, *evaluation of the circulation of the feet* (see p. 181), and a *roentgen ray search for calcified vessels*. A tourniquet test will often detect undue *capillary fragility*—especially in patients having retinal hemorrhages. A recording of the *blood cholesterol* (venous blood with patient in fasting state) may be of value for comparative purposes. The presence or absence of *albuminuria* should be noted and also the range of the *specific gravity of sugar free urine*. The *blood urea nitrogen* concentration is determined if *albuminuria* and arterial hypertension are present.

Arteriosclerosis Obliterans (Atherosclerosis). The changes in the intima of the arteries which characterize this disorder make it the outstanding vascular complication of diabetes. Intimal plaques form on the side of the medium sized arteries causing a localized narrowing of the lumen which predisposes to occlusion especially of the coronary arteries and the arteries of the distal extremities hence the term *arteriosclerosis obliterans* which, because of its descriptive connotation, is receiving general adoption.

The obliterative nature of the atheromatous changes by reducing the size of the lumen of the artery, reduces the capacity of the vessel to deliver blood to the peripheral tissues in normal amounts. Varying degrees of obliteration may exist for long periods without causing symptoms but, as the lumen of the artery is progressively infringed upon, eventually symptoms, notably anginal pains and intermittent claudication are noted on occasions of increased physical activity. Still later, the patient becomes more and more conscious of the impaired circulation as indicated by coldness and disturbances in sensation in the feet, and finally with complete occlusion, localized death of tissue occurs. This is exemplified in the case of myocardial infarction or of gangrene of an extremity.

The precipitation of the acute complication is usually on the basis of a thrombus occurring in the vessel where its wall is deformed by eccentric atheromatous plaques. Insufficiency of the coronary circulation and gangrene are dealt with under acute complications (see p. 212).

The mechanisms associated with these changes are more readily under

stood if it is realized that arteriosclerosis is not a static condition but one with periods of exacerbation and periods of quiescence. It comprises localized intimal thickening in which necrosis takes place and cholesterol and other lipids are laid down in the diseased site. These subsequently are dissolved out, leaving clefts. The resulting softened mass is the so called *atheroma*. The atheroma is subject to cellular exudation, vascularization of the margins, organization and, in the advanced lesion, hemorrhage. Destruction of the media occurs in advanced cases and calcification of the plaque is common. Atherosclerosis bears a direct relationship to *obesity, to the duration of the diabetes and to hypercholesterolemia with poorly controlled diabetes*.

Monckeberg's Sclerosis. Calcification of the media of the muscular arteries is the salient feature of Monckeberg's sclerosis. It is not as common as atherosclerosis in diabetic patients but is seen more frequently and in more advanced stages in these patients than in nondiabetic individuals. It gives to the palpable artery a beaded contour of stony hardness—the so called *pipestem artery*. Calcification of the media may occur in any artery but involvement of the vessels of the distal extremities is the most common.

Arteriolar sclerosis. In this form of arteriosclerosis hyaline material is laid down in the walls of the arterioles as described on page 62. It, also, occurs more frequently and at an earlier age and to more severe degree in diabetic than it does in nondiabetic subjects. Of diabetic patients over fifty years of age arteriolar sclerosis involving renal vessels is present in 77.6 per cent or about five times as frequently as in nondiabetic controls. Arterial hypertension is more constantly associated with arteriolar sclerosis than it is with atherosclerosis.

Treatment for Chronic Degenerative Vascular Complications of Diabetes. The chief aim in treating patients having chronic degenerative changes in the vascular system is to restore disturbed physiologic processes to normal, or as nearly to normal as is practicable, and in this manner provide relief from or reduce as much as is possible, the subjective symptoms and clinical evidences of the disease. In so doing it is hoped that the tendency of the disorder to become worse will be allayed.

Correction of Disturbed Physiologic Processes. Disturbances in the physiologic processes and the practicable means of dealing with them are as follows:

1. HYPERGLYCEMIA AND GLYCOSURIA. The treatment is as outlined on page 103, except that it is advisable to adjust the diet and insulin more conservatively than in patients having minimal or no demonstrable changes in the vascular system. A gradual decrease of the hyperglycemia—over a period of several weeks—is preferable to rapidly attained control. Hypoglycemic reactions should be guarded against, as they predispose to occlu-

sion of the coronary arteries in these patients. Fortunately, these patients usually have a wide margin of safety permitting good control of the diabetes without undue risk of hypoglycemic reactions.

2 HYPERCHOLESTEROLEMIA AND EXCESSIVE CHOLESTEROL ESTERS AND LIPEMIA The high incidence of insufficiency of the coronary arteries in nondiabetic patients who have hypercholesterolemia and those who have xanthomatosis emphasize the part that like disturbances in physiology may play in the presence of diabetes. A reduction of the lipid transport in the blood is most readily achieved (a) when obesity is corrected and (b) when a liberal carbohydrate intake is permitted. Allowances of 250 to 335 gm of carbohydrate in the daily diet usually are necessary to reduce the hypercholesterolemia appreciably and to reduce the metabolism of fat sufficiently to overcome the hyperlipemia. A low intake of fat—below 75 gm, and preferably below 50 gm daily—is desirable. It is probable that when the complicated and variable mechanisms involved are solved it will be all too obvious that most diets, recommended by authorities on diabetes, contain too little carbohydrate and too much fat. (c) We advocate protein in excess of 100 gm.

3 OBESITY Correction of obesity will tend to prevent as well as alleviate the progressiveness of the degenerative changes in the arteries. It is accomplished as outlined on page 105 except that when advanced arterial disease exists it is preferable to permit as liberal an intake of carbohydrate as is practicable, e.g., 250 gm in a diet containing 100 gm of protein and 1700 calories. Circulatory difficulties are much more common in the overweight than in individuals of normal weight. Atherosclerosis is most common in the obese and relatively uncommon in those who are underweight, and undernutrition militates against the development of the complication in man and tends to protect experimental animals who are not so protected if in a well nourished state. Also, based on autopsy evidence, a thin subject of fifty years of age usually has less atherosclerosis than a forty year old fat person (Wilens).² Wilens has shown that a reduction in body weight causes regression of atheromatous changes and a reduction of the lipid content of atheromatous plaques in a significant percentage of cases. The state of nutrition plays an important, if not an essential, part in the speeding up and slowing down of this serious complication of diabetes. An optimum state of nutrition with the body weight a trifle below the standard weight after thirty five years of age is a goal aimed at too infrequently and much less frequently is it attained.

The reduction in body weight in cases of diabetes has, in our experience, a favorable influence on high arterial hypertension in diabetic than it has in nondiabetic patients. The correction of hypertension is of special value in subjects with atherosclerosis and arteriosclerosis. Uncorrected, the hypertension accelerates these degenerative processes.

Restriction of the salt intake is of outstanding value. This measure attains even greater importance if the hypertensive obese diabetic patient displays evidences of circulatory decompensation. The benefits of this measure were observed in 1926 in dealing with circulatory failure in nondiabetic subjects.³

Thoracolumbar sympathectomy is recommended when the indications for it are clear. These are:

- 1 The patient is not over fifty years of age
- 2 There are clear evidences that the hypertension is progressive
- 3 There is no nitrogen retention in the blood
- 4 The heart is not markedly enlarged—certainly not more than a 50 per cent increase above the normal dimensions and with no evidences of congestive heart failure
- 5 The responses to amylal cold pressor (if applicable) and tetra ethyl ammonium chloride (etamon) tests, and the exclusion of a pheochromocytoma by the dibenamine hydrochloride and benzodioxane tests indicate that one can reasonably anticipate a beneficial outcome. Good results and vice versa have followed despite poor responses to these tests but in general they give valuable impressions as to the course to pursue
- 6 When responses to conservative treatment—reduction of the obese salt free diet, mild sedation and psychiatric therapy—are unsatisfactory
- 7 When a complete clinical appraisal indicates that the patient without a sympathectomy has a life expectancy of not more than five years

These may appear to be severe terms upon which to decide concerning a sympathectomy but if adhered to needless sympathectomies will be avoided and on the other hand the patient who derives little or no benefit from other therapies and is a fit subject for operation will not be deprived of the possible advantages which it has to offer. It has been estimated that approximately 4 per cent of hypertensive patients are suitable candidates for sympathectomy.

II Diseases of the Coronary Arteries Complicating Diabetes

Occlusion of the coronary arteries has far outstripped other causes of death in diabetic patients at the Pennsylvania Hospital. The frequency of this serious complication is as frequent indeed in the past two years has been more frequent in the female than in the male diabetic patients. This is of great interest as, in the nondiabetic population, this complication occurs in male and female between the ages of fifty one and sixty in approximately a 5 to 1 ratio.⁴ There is an increasing incidence of diseases of the coronary arteries in diabetics and especially in this true for the female patients. At one time during the past year we had on a general medical ward of forty beds, five female diabetics each with an occlusion of a coronary artery. Each was overweight, four were known to have had increased

arterial blood pressure, one had no previous history of diabetes, and four patients had a long-standing uncontrolled diabetes

The main known factors at work in increasing the prevalence of disease of the coronary arteries in diabetic patients are (1) the extended duration of the diabetes, the degree of severity and control of the diabetes—mild diabetes of short duration is not as likely to be complicated by occlusive disease of the coronary arteries as when the disease is of long duration, of a severe degree and poorly controlled (2) The increased span of life for diabetics has influenced unfavorably the incidence of disease of the coronary arteries (3) *Excessive concentration of cholesterol and other lipids in the blood is associated with a much higher frequency of atherosclerotic changes and occlusive phenomena than when these chemical abnormalities are absent* (4) *Arterial hypertension*, (5) *obesity*, (6) *excessive use of tobacco* and (7) *hypoglycemic reactions* predispose to occlusion of the coronary arteries which have undergone marked atherosclerotic changes. It seems most probable that this is the result of an "alarm reaction" and bears a relationship to the increased amount of epinephrine in the circulation which occurs with the development of a hypoglycemia

Patients with occlusive disease of the coronary arteries are predisposed to sequelae similar to those seen in the nondiabetics but the sequelae are likely to appear earlier and they tend to be more rapidly progressive in diabetic individuals. They include myocardial decompensation, heart block, auricular and ventricular fibrillation, complete occlusion of a coronary artery, and embolism

There is no satisfactory yardstick with which to measure the efficacy of prophylactic measures in the individual case but it is our impression that benefit accrues from control of the diabetes, from reduction of hypercholesterolemia through the agency of liberal carbohydrate and protein and low fat allowances in the diet, from the correction of obesity and hypertension, from the restriction or complete elimination of the use of tobacco and by practicing great care in preventing hypoglycemic reactions

An understanding internist who has a comprehensive knowledge of the patient's problems, mental and physical, is in the best position to give effective reassurance and guide the patient into gracefully accepting the situation in which he finds himself and in helping him institute an optimum regimen of living

Treatment Insufficiency of the coronary circulation may be manifest by attacks of *angina pectoris*, the treatment for which comprises

1 Gradual control of the diabetes—this takes several weeks if the risk that attends rapid control is to be avoided

2 The correction of obesity. A low calorie diet is employed and when the weight has reached a satisfactory level, the diet is increased, using liberal protein and carbohydrate with low fat contents, e.g., protein 90 gm., carbohydrate 275 gm., and fat 59 gm. (1900 calories)

3 Vasodilators—nitroglycerin, 0.3 mg ($\frac{1}{2}$ 200 gr) and aminophylline,

0.5 gm ($7\frac{1}{2}$ gr) are most commonly used for the alleviation of an attack of angina pectoris. Patients who are subject to attacks of angina should never be without nitroglycerin, which may also be used as a prophylactic measure when the patient's attack pattern is known. To prevent recurrent attacks the following remedies are recommended: theobromine calcium,* 0.5 gm ($7\frac{1}{2}$ gr) and phenobarbital, 10 mg ($\frac{1}{6}$ gr) four times daily, or papaverine hydrochloride, 60 mg (1 grain) four times daily.

4. Restriction of physical activity—climbing exercises and brisk walking against a strong or cold wind especially are to be avoided. Absolute physical rest during an anginal attack will usually bring relief.

5. The use of tobacco is interdicted.

6. Reduction of the total body metabolism by administering sufficient amounts of 6-propyl thiouracil to keep the basal metabolic rate between minus 10 and minus 25 per cent. Ordinarily this is achieved with 50 mg four times daily, though larger initial amounts may be needed and smaller maintenance doses may suffice. This measure is recommended as an especially satisfactory remedy but its use should be restricted to intractable cases of angina pectoris.

Acute Occlusion of a Coronary Artery. The treatment employed at the Pennsylvania Hospital and supplemented by other measures that may be indicated, to give relief from pain, to put the patient at rest mentally and physically, is as follows:

1. Complete rest in bed—patient is fed and not allowed to bathe, or turn or get on a bed pan without help.

2. The diet is liquid, soft or regular as tolerated. It is divided into four equal and small meals as for other acute complications (see p. 217).

3. Mineral oil 30 cc. and fluidextract of *cascara sagrada*, 4 to 8 cc., is given daily at bedtime if needed for daily evacuation.

4. Papaverine hydrochloride, 60 mg (1 grain), is given orally every four hours.

5. Morphine sulfate is used in amounts sufficient to provide relief from pain—usually 15 mg ($\frac{1}{4}$ grain) or 30 mg ($\frac{1}{2}$ grain), given hypodermically.

6. Heparin, 50 mg, is given at once intravenously and repeated every six hours until the Dicumarol therapy† has reduced the prothrombin time to 30 to 20 per cent of normal.

7. Dicumarol is administered orally as follows:

300 mg. on the first day.

200 mg. on the second and third days.

50 to 300 mg. daily thereafter as needed to maintain a prothrombin time between 20 and 30 per cent of normal until ambulation is permissible—usually three to five weeks—at which time the anticoagulant therapy is discontinued.

* Commercially available as Purinal and Parobarb—both supplied by A. J. Parker Company, Philadelphia.

† A more rapidly effective anticoagulant, Tromexan—a brand of ethyl bis-coumate—is showing considerable promise and may replace Dicumarol.

Studies 1 Prothrombin time is determined daily until the patient's tolerance to Dicumarol is known. Thereafter the test is done on alternate days or every third day.

2 An electrocardiogram and an erythrocyte sedimentation rate are secured at weekly intervals.

3 Close clinical observation—several times daily. Readings of the blood pressure are taken twice daily until convalescence is under way.

Reduction of the body weight, while reparative mechanisms are at work is not recommended but when convalescence is well established—usually four or five weeks after the acute onset, a reduction program is advised for the patients who are overweight.

Treatment for the diabetes during the acute phase is the same as for an acute infection (see p 217), until the patient is free from pain and can adopt a regular meal schedule.

III Circulatory Disturbances in the Legs and Feet

Appraisal of the Circulation Failure of the arterial circulation to deliver adequate amounts of blood to the tissues results from a narrowing of the arterial lumen as occurs frequently in the peripheral vessels of the older diabetic patients. Arteriosclerosis obliterans occurs eleven times more frequently in diabetics than in nondiabetic controls.⁶

The evaluation of the circulation is in reality the determination of the degree of patency of the lumen of the artery at its narrowest point and it is upon this feature that the prognosis and therapy depend.

Symptoms Mild degrees of arteriosclerosis obliterans cause no symptoms but as the condition progresses the sensation of coldness in the affected extremity becomes apparent. A decrease in the muscular endurance and impaired sensitivity to minor injuries and an accompanying partial anesthesia appear subsequently. The symptoms of neurologic origin are to be evaluated carefully if the pitfall of attributing a diabetic neuritis to a deficient circulation and not to a more widespread diabetic neuropathy is to be avoided. The physical signs of circulatory inadequacy must support the diagnosis of an ischemic neuritis. Otherwise, the symptoms are more likely to be due primarily to metabolic degenerative abnormalities in the nerves as occur in the neuropathies associated with diabetes (see p 202).

Intermittent claudication, first appearing after brisk walks for considerable distances, appears as a frequent symptom. A severe grade of arterial obstruction is present when this symptom is provoked by walking 20 to 30 yards and at a slow pace. If comparative studies are being done from time to time, the same distances and speeds in the various observations are maintained. A short rapid walk will provoke intermittent claudication when a slow walk for a long distance may not be accompanied by this distressing symptom.

Pain—severe and persistent—in the feet and especially in the digits

while at rest, and especially at night, indicates advanced vascular obstruction, provided neuropathic changes are not responsible. The onset of rest pain may be insidious and progress gradually or it may be sudden with the complete occlusion of an artery. Rest pain is common in the region of an ulcer or of a gangrenous area.

Pain due to an ischemic neuritis is of wider distribution and the discomfort is variable in nature and intensity and has burning or shooting characteristics.

The onset of pain in an extremity having a poor circulation may follow a minor injury to the foot. In this case the local reaction exerts a demand for circulation which the circulatory means at hand is unable to meet. The situation may be made worse by local vasoconstriction. This is a common occurrence preceding the appearance of gangrene although gangrene may appear spontaneously with or without pain. Frequently a vesicle is the first local sign of gangrene.

Physical signs: On inspection the dependent limb with a normal circulation shows no discoloration but with advancing arteriosclerosis obliterans the affected member becomes bluish red when in the dependent position. This discoloration fades proximally over the dorsum of the foot but in some cases it extends halfway to the knee or even higher. The prompt change to a cadaveric pallor following the elevation of the foot for two minutes and a slow—in excess of thirty seconds—return of the cyanosis on returning the foot to a dependent position, combine to indicate an advanced degree of obstruction in the arteries. These postural changes are highly significant when present. The development of collateral circulation may prevent these color changes even though the large vessels are pulseless. It is significant that arteriosclerosis obliterans involves chiefly the larger vessels and it is not infrequent that the capacity for arteriolar dilatation is not greatly impaired. Marked pallor may follow the sudden occlusion of an artery of medium size.

Trophic changes in the skin, muscles and nails may be apparent on inspection. Ulceration and gangrene with or without apparent infection may be present. Evidences of a pyogenic infection, a lymphangitis and of *epidermophytosis* are important. Local injuries, and especially fissures that result from fungus infections afford a ready portal of entry for other infective agents.

Gangrene involves the more prominent parts of the feet as a rule—the toes, the heel, the prominence of the metatarsophalangeal joints of the small and great toes, the dorsum of the foot and the malleolar regions.

Palpation: The tips of the toes are cold in advanced degrees of obliterative arteriosclerosis. The involved foot may be cold in contrast to its fellow. A difference in temperature in the two feet is especially significant when both have been exposed to the same environmental temperature. Whether this coldness is due to a functional or organic obstruction is determined

by special studies of the skin temperature. It is important to detect impaired or absent pulsations in the *dorsalis pedis*, *posterior tibial*, *popliteal* and *femoral* arteries. Pulsations of the *dorsalis pedis* arteries may be absent because of congenital anomalies but if, in addition, the *posterior tibial* and *popliteal* pulsations are impaired or absent, *arteriosclerosis obliterans* is almost certain to be the cause. *We consider the degree of pulsation and changes in temperature of the tips of the toes as the most important of the clinical means of appraising the circulatory efficiency of a limb.* Poor tone of the muscles and impaired or intensified cutaneous sensitivities are among the less specific results of an impaired circulation.



Fig. 21 Calcification of the arteries and osteoporosis in the feet of a diabetic patient

Ulcers over a joint, or soft corns between the toes are common fore runners of arthritis or osteomyelitis due to pyogenic organisms. Careful physical estimation and roentgen ray studies of these possibilities will often explain chronic discharging sinuses and failures in healing.

The clinical evaluation of the state of the circulation is superior to special tests. The latter have an important place in supporting clinical findings however. *In general the circulation is good if the patient does not complain of pain in the extremities, if there are no color changes, if there is good pulsation in the dorsalis pedis and posterior tibial arteries, and if the tips of the toes are warm.* Warm toe tips in the absence of good pulsation of the peripheral arteries is a sign of a good collateral circulation. *Contrariwise the circulation in the limb is severely impaired if rest pain and intermittent claudication are prominent, if the bluish red cyanosis (rubor) of the dependent foot gives way to a cadaveric pallor when the foot is elevated, if the tips of the toes and the foot are persistently cold and if there is ab*

sence of pulsations in the peripheral arteries of the foot—the dorsalis pedis and posterior tibial arteries

Special Tests These studies are used selectively when needed to support clinical impressions. Usually they are not necessary.

ROENTGENOGRAPHY This study aids in determining the degree of and position of calcified areas in the arterial wall. It should include not only the foot and leg but also the thigh, as obstructive lesions in the femoral arteries are frequent. Patchy, dense deposits of calcium causing a marked degree of obstruction, identified by roentgen ray studies, may in some cases influence the selection of the site of amputation.

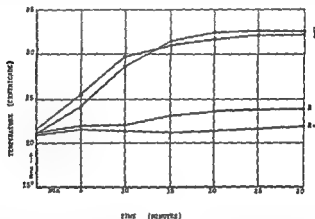


Fig. 22 Skin temperature vasodilatation test. The increase in temperature in the left foot upon immersion of the hands and arms in hot water indicates a high degree of spastic vasoconstriction. The absence of a similar response in the right foot is indicative of organic vascular occlusion.

Roentgenograms are of value also in detecting osteomyelitis of the small bones of the feet and in assaying the degree of osteoporosis and destruction of bone in the rare case of neurotrophic foot (see p. 207).

SKIN TEMPERATURE STUDIES These studies tend to (a) confirm the clinical diagnosis and (b) afford information regarding the relative degree of functional arterial spasm and of organic arterial occlusion. The temperatures of the skin over the tips of the toes, the dorsum of the affected foot and various other levels are taken, the patient having been in a room the temperature of which is approximately 20° C (68° F) for one-half hour. These readings are recorded and compared with those taken one hour after both arms and hands have been immersed in hot water, 43 to 45° C. This schedule, as advocated by Gibbon and Landis,* causes a definite reflex vasodilatation and a rise in temperature in the distal extremities from a normal temperature of about 21.7° C on the toe and 30.2° C on the sole of the foot, to 31.5° or 34.5° C if the vascular supply is normal or if occlusion

has been due to vascular spasm (Fig 22) There is little or no rise in the skin temperature of the feet in the event of an advanced occlusion of the arteries due to organic changes This test is especially desirable if a sympathectomy is considered It identifies the vascular spastic type of occlusion in which the operation holds promise of success in contradistinction to the organic occlusive vascular disease, in which sympathectomy would be not only valueless but dangerous Satisfactory evaluation of the alterations in circulation is obtained without the more radical nerve-blocking procedures, notably spinal anesthesia or the injection of the peroneal nerve Refinements in the execution of this test have detracted from its value and hence are not included

PLANTAR ISCHEMIA TEST This test, popularized by Samuels,⁷ is carried out with the patient in the reclining position The patient raises the foot being studied to an angle of 45 degrees, in which position he flexes and extends the foot rapidly for one minute Obstructive arterial disease of a severe degree is indicated by the development of an alabaster like color of the plantar surface of the foot There is little or no change in color if the arterial circulation is normal This test when positive indicates a slowing of the circulation as does the elevation and dependency test presented on page 185

Other Tests Oscillometric studies, arteriography, histamine flare test intradermal saline wheal test and the fluorescein test are listed because they appear in medical writings frequently and not because of their clinical value We do not employ them because they either add little or no information and are unnecessary, or mislead or carry risk out of proportion to the information they might reveal We do not mean to detract from the value of these tests as research procedures

Differential Diagnosis *Arteriosclerosis obliterans* as it is encountered in diabetes characteristically develops occlusive manifestations in patients over forty years of age it involves the lower extremities almost entirely, thrombophlebitis is not a feature of the disorder, there is calcification of the arteries in 69 per cent, males constitute 83 per cent of those afflicted,⁸ 34 per cent have an associated hypertension, 20 per cent of Allen's patients had diabetes, and elevated blood lipids is a common finding

In contrast thromboangitis obliterans, with which arteriosclerosis obliterans might be confused, practically always occurs in male subjects under fifty years of age, 40 per cent have involvement of the upper extremity, 40 per cent have thrombophlebitic phenomena, there is no calcification of the arteries, diabetes is a rare complication and the blood lipids are usually normal

Diabetic neuropathy may co exist with arteriosclerosis obliterans but numbness, lightning pains and ulcerations may be due to neurotrophic changes in the presence of warm toe tips and excellent pulsation of the peripheral arteries Absent or sluggish tendon reflexes and an impaired

vibratory sense over the distal extremities afford valuable clues in identifying the neurologic nature of the disorder in contrast to the predominantly vascular changes already presented

There should be no difficulty in differentiating *gout*, *arthritis*, *sciatica*, the *burning feet* of *malnutrition states*, *erythromelalgia* and *thrombophlebitis* if the history is carefully taken and if the physical examination is complete

IV Gangrene

Gangrene in an extremity of the diabetic patient occurs primarily because of the occlusive nature of arteriosclerosis obliterans (Fig 13) and the resulting incompetency of the arterial circulation in meeting sudden or increased circulatory demands. The precipitating cause of gangrene is usually injury which may be due to trauma, infection or extremes of temperature. Thrombotic or embolic phenomena in an atheromatous vessel also may be the exciting cause of gangrene. Any combination of events that will increase the need for circulation or that will obstruct the supply route is sufficient to deprive the tissues of nutrition adequate to retain their viability.

The onset of gangrene may be sudden and painful, as occurs in the abrupt cutting off of the circulation by an arterial embolus. Or, there may be no pain and a vesicle may be the first ominous sign of local capillary damage to be followed by changes in color from the normal to a dark blue-gray or black in the underlying tissues. Infection, with its complicating hyperemia and lymphangitis, is a common complication. It may progress rapidly or slowly and the speed with which local death of tissues proceeds as a result of infection will depend on the degree of the devitalization of the tissue and the virulence of the infection. Infection tends to cause local inflammatory changes with an exudative lesion and accounts for more pain than is usually the case when infection is absent. In the latter instance the gangrenous area may be relatively painless and become demarcated, hard, dry, mummified, shriveled and black.

In appraising the clinical state of a diabetic patient who has a gangrenous area special attention is given to the degree of concomitant degenerative changes, notably in the coronary, cerebral, renal and retinal circulations. These patients are usually over fifty years of age and have degenerative changes in their arteries of a degree seen in control nondiabetic subjects who are at least ten years older.

Prevention. More often than not arteriosclerosis obliterans is present to an advanced degree when these patients seek treatment. Nevertheless, there will be ample opportunity to practice prophylaxis though it is not always as successful as we would have it be. The preventive measures are

A. *Control of the Diabetes*

B. *Correction of Hypercholesterolemia if Possible for this purpose*

eral amounts of carbohydrate (250 to 335 gm) with low fat (less than 75 gm) and ample protein ($\frac{5}{8}$ gm per pound of the ideal body weight) are allowed

C Weight Regulation It is necessary to secure and maintain a body weight a trifle below the standard weight

D Special Care of the Feet Details in hygienic care of the feet are dealt with in some detail on page 173

E Symptomatic Relief from Pain

F Local and Systemic Treatment for Ulcers and Infections In addition to local therapy bacterial cultures are taken from ulcerating areas and from discharging sinuses and the sensitivities of the pathogenic organisms to the various antibiotic agents are determined. This measure usually permits a specific attack on the offending organisms. Too much emphasis cannot be placed on the value of complete bacteriologic evaluation of these infections. Lives and limbs will be saved if such studies are done in every case of bacterial infection. Furthermore, cultures of the blood are taken if the patient is febrile and has an increase in the number of leukocytes in the blood

G Physical Therapy The circulation in the legs and feet may be improved by the following measures: (1) Sanders oscillating bed, (2) intermittent suction and pressure, (3) intermittent venous occlusion, (4) Buerger's exercises, (5) application of heat to hands and arms, and (6) thermoregulated foot cradles. Applications of heat, without appropriate automatic thermoregulation, to the legs and feet are contraindicated. Probably no other single exciting cause of gangrene outnumbers that of the unwise application of heat. Heat, under normal conditions, causes vasodilatation and hyperemia in the limb but with an impoverished circulation it does not exert this effect but rather tissue damage occurs, probably due to a local increase in the tissue metabolism without a commensurate increase in the circulation.

SANDERS OSCILLATING BED⁹ This is the most satisfactory form of the mechanical methods of therapy. The treatment may be continuous or intermittent, e.g., one hour three times daily depending upon the degree of relief from pain that is achieved. This form of therapy is contraindicated in the presence of a bacterial infection with a cellulitis.

SUCTION AND PRESSURE THERAPY¹⁰ This method^{*} has suffered in popularity in recent years but is nevertheless helpful in some cases. It is contraindicated in the presence of collections of purulent material, acute bacterial infections and cellulitis. Suction amounting to 80 to 120 mm of Hg is applied for twenty five seconds alternating with a positive pressure of 40 to 80 mm of Hg for five seconds. At the outset of the treatment pressures alternating from minus 80 to plus 40 mm of Hg and progressing to minus 120 to plus 80 mm are used according to the relief achieved.

^{*} Equipment is manufactured by The Burdick Corporation, Milton, Wis.

Treatments are given one to two hours daily, decreasing as improvement is established to three treatments, and finally one treatment per week.

INTERMITTENT VENOUS OCCLUSION ¹¹ A cuff is fitted above the knee and is inflated to a pressure of 70 to 80 mm. of Hg, obstructing the venous return for one, two or three minutes, followed by a like period of release. When a reactive hyperemia occurs appreciable relief from intermittent claudication results. The treatment is continued for one to two hours daily. It is contraindicated in cases of venous insufficiency.

BUERGER'S EXERCISES ⁸ The great advantage of this form of therapy is that it can be carried out by the patient without intricate apparatus (Fig. 23) at home and for long periods. The patient, lying on his back, raises

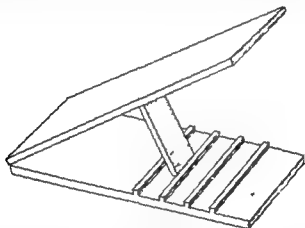


Fig. 23 A Buerger board

one or both feet at an angle of 15 to 60 degrees, and allows them to rest on an adjustable board until the feet are quite blanched or until the foot becomes painful. This usually requires about one minute if foot exercises are conducted in this position and somewhat longer, up to three minutes, if the feet are passive. The patient then assumes the sitting position with the legs hanging over the edge of the bed until a reactionary hyperemia develops or until pain is experienced in the legs or feet. After two to five minutes in this position a rest period for about three minutes is allowed in the horizontal position. This cycle may be repeated several times daily at first and increased gradually until the exercises last from one half to one hour daily. Dramatic improvement is not to be expected.

APPLICATION OF HEAT TO HANDS AND ARMS In cases of vasospasm an

* A Buerger board which is adjustable to different angles is made simply by having two boards, each $\frac{1}{2}$ inch thick, 30 inches long and 12 inches wide hinged at one end with a supporting prop between, which is adjustable to fit on various cleats according to the angle desired.

appreciable increase in the temperature of the feet follows the application of heat—hot water bath or electric pad—to the hands and arms. This is a simple therapy that patients can carry out themselves. Also, this method enhances the value of the suction and pressure therapy when the two treatments are given simultaneously.

THERMOREGULATED FOOT CRADLES Foot cradles without thermostatic controls are dangerous devices and should not be used. However, great relief is frequently secured by having the feet and legs in a foot cradle, the temperature of which is maintained at 90° F (32.2° C).

H Vasodilator Drugs Several drugs and several combinations of therapy are available for trials. Some may be effective in a case in which others give no benefit. In any case most benefit may be anticipated when the element of vasospasm is great, and least, or no benefit, when organic arterial obstruction is of a severe grade.

Nicotinic acid, 50 to 200 mg four times daily in conjunction with papaverine hydrochloride, 0.1 gm (gr 1½) three times daily, both given by mouth, is sometimes surprisingly helpful.

Tetra ethyl ammonium chloride (etamon) by blocking ganglia of the autonomic nervous system has produced the same degree of vasodilatation as nerve block, spinal anesthesia and sympathectomy.¹² Hence, this drug is used to determine the relative degrees of vasospasm and of organic ob-

given intravenously in doses of 0.1 to 0.5 gm. The infusion (1 to 5 cc) is given very slowly and the patient is kept at rest for one hour after its completion. The same precautionary measures are taken when intramuscular injections of 0.8 to 1.0 gm are given—one-half of the dose is given in each buttock. A marked drop in the blood pressure may follow the injection of etamon within fifteen or twenty minutes, a reaction which can be controlled, if need be, by administering ½ cc of epinephrine subcutaneously.

This remedy is often effective in improving the circulation and in relieving pain but the benefit is too evanescent to be of clinical value.

Dibenamine hydrochloride has a blocking action on the sympathetic nervous system as well as a neutralizing effect on epinephrine in circulation. Both of these actions tend to cause vasodilatation, an effect which continues from twenty-four to ninety-six hours. Dizziness and fainting sensations may be experienced on rising from the lying to the standing position after the drug is given. These symptoms are associated with a marked reduction in the blood pressure.

Dibenamine is available for oral therapy but the intravenous route yields more satisfactory results. In this manner 5 to 7 mg per kg of body weight are given in 300 to 500 cc of normal saline solution.

Priscol is reported to exert a blocking effect upon the sympathetic vas-

cular receptors and a direct histamine like effect upon the smaller vessels.²² It is a beneficial drug in cases of vasospasm when administered in doses of 50 mg four times daily—by oral, intramuscular or intravenous routes. Our experience with this remedy in the treatment for organic occlusive vascular disease has been small and disappointing.

Tissue extracts, notably Depropanex, have reputed value in relieving intermittent claudication. Depropanex is given daily in doses of 5 cc intramuscularly. In a very limited experience with this preparation we have concluded that an equal degree of relief will ensue if patients subject to attacks of intermittent claudication make an inviolable practice of walking slowly.

Our experience with diethyl oxide (ether) as a vasodilator is nil but a review of the literature leads one to believe that it is of little practical value. At best, the vascular drugs give disappointing results when severe grades of organic occlusive arterial disease are present.

Other Measures THE LIGATION OF THE FEMORAL VEINS has in several instances in our experience given abrupt relief from intractable pains and the relief was attended with an increase in the warmth of the skin in the affected extremities. This is not a widely used procedure but the response is so striking even in severe grades of arteriosclerosis obliterans that it deserves consideration when conservative measures fail and amputation seems to be the last resort in the attempt to alleviate pain. The beneficial response is apparently due to a slowing of the venous return and to an increase of blood in the impoverished area.

EXERCISE Mild forms of exercise are helpful. Patients with intermittent claudication must, however, be instructed to walk slowly. Buerger's exercises are recommended.

OCCUPATION Occupation and other activities which present special risk of injury to the feet should be given up in the face of advanced occlusive arterial disease of the legs and feet.

SYMPATHECTOMY In carefully selected cases, and in the face of failure of conservative methods to relieve pain and particularly that of intractable intermittent claudication and in cases in which the element of vasospasm is considerable, sympathectomy may offer some benefit. We employ this measure infrequently.

Care of the Feet in the Prevention of Gangrene General hygiene of the feet is dealt with on page 173. Correction of abnormalities, i.e., calluses, corns, fungus infections (epidermophytosis), is as follows:

CALLUS FORMATION Calluses are corrected by soaking feet each evening in warm, not hot, soapy water for twenty minutes and then rubbing surface tissues off with gauze. Measures to prevent subsequent callus formation will depend on the cause. e.g., corrective supports for poor arches, foot exercises—especially the practice of picking up twenty medium sized marbles with the toes night and morning—and properly fitting footwear, hose and shoes. A leather bar across the bottom of the shoe—correspond

ing to the position of the heads of the metatarsal bones—is often helpful in redistributing pressure exerted by the weight of the body

CORNS Corns are caused by improperly fitted hose and shoes. Properly fitting footwear is the first requisite of therapy. The cornified layer is pared off with great care, preferably by a chiropodist, but at least by an experienced person other than the patient, and one who has good vision, works in a good light and exercises extreme caution against cutting into living tissue. Distribution of the local pressure is secured by employing appropriate felt pads. "Soft corns" between the toes are dealt with by wearing shoes that do not compress the toes and by keeping the toes separated with lamb's wool. "Soft corns" are especially hazardous as osteomyelitis is frequently an early complication.

PREVENTION AND CORRECTION OF EPIDERMOPHYTOSIS Good foot hygiene as already outlined (p. 173) is essential in dealing with mild manifestations of epidermophytosis, as indicated by a macerated or a parboiled appearance of the skin between the toes with itching. Control of this disorder is usually secured promptly by applying a thin film of fungicidal foot powder, containing zinc undecylenate, undecylenic acid and talc* over the affected areas and between the apparently unaffected toes after each bathing until the condition is controlled and thereafter, once weekly.

When fissures are present the following preparation is applied daily

Rx Salicylic acid	35 gm
Benzoic acid	70 gm
Castor oil	300 cc
95% ethyl alcohol	1800 cc

With correction of the fissure, treatment with foot powder is begun, or resumed.

Or, in place of the prescription presented above, a fungicidal ointment† may be used daily.

For the severe cases with acute vesicular or bullous eruptions and with secondary infections, the feet are soaked in a 1:8000 solution of potassium permanganate for thirty minutes three times daily, for not more than one week. As the acute phase subsides the prescription (salicylic acid, benzoic acid, castor oil and ethyl alcohol) included above, or a stronger keratolytic agent such as one half strength Whitfield's ointment, is used until it appears advisable to change to the foot powder for long term therapy and prevention.

The prevention and correction of epidermophytosis assume importance of considerable magnitude as measures against the onset of gangrene. Untreated epidermophytosis provides portals of entry for secondary infection which is often sufficient to tip the balance unfavorably when the local cir-

* Available commercially as Desenex Powder

† Available commercially as Desenex Ointment

ulation is adequate in the absence of infection but insufficient to meet the increased circulatory demands that attend an infectious process.

Treatment for Gangrene. The therapy for gangrene due to occlusive vascular disease in a diabetic is conducted in cooperation with a surgeon who has a special interest in diabetes and who is especially skilled in the management of these patients.

Many factors may influence therapy but the most important are (1) the degree of efficiency of the circulation and (2) the presence of infection. Conservative nonoperative treatment is justifiable if the area of gangrene is well demarcated and superficial, if the tips of the toes are warm and there is good pulsation in the dorsalis pedis and the posterior tibial arteries, when the extremity retains normal color on elevation and when in the dependent position. The first principle is to do no harm. The active therapy comprises (a) Control of the diabetes but not so strictly that hypoglycemic reactions are likely. (b) Eradication of infection. This is done by gentle release of confined pus from which a culture is grown and the sensitivity of the pathogenic organism to penicillin, aureomycin, chloromycetin, terramycin, streptomycin and neomycin is determined. This determination of the sensitivity of the organism we consider to be a highly important procedure, as it usually gives the clue to which antibiotic or combination of antibiotic agents can be expected to give the most benefit. Between the time that the culture is taken and the report on the sensitivities is received we give procaine penicillin, 150,000 units, intramuscularly daily. Thereafter, suitable doses of the appropriate antibiotic agent are given. (c) Where crusts of dried exudates are present or without evidence of trichophyton infection the affected foot is soaked in a solution of potassium permanganate 1:8000, the temperature of which should not be lower than 90° F. (32.2° C.) and not higher than 105° F. (40.5° C.) for one-half hour three times daily. (d) Subsequent to the foregoing local treatments local applications of Furacin or tyrothricin have been valuable. (e) Improvement of the arterial circulation in the limb may be accomplished by intermittent venous occlusion if there is no venous insufficiency. Barring contraindications, as already noted, other methods may be tried (see p. 190). The presence of an acute infection calls for complete rest of the affected part and as a result most of the measures that are of use prophylactically are to be avoided when infection is present. (f) Ligation of femoral veins has yielded gratifying results in a few carefully selected cases in which pain was predominant and in which indolent gangrenous ulcers were at a standstill. Occasionally the results from this simple procedure are so spectacular that we commend it for more frequent consideration than it generally receives.

Amputation. The incidence of amputations has decreased with the growth of sulfonamide and antibiotic therapy. Furthermore, when amputation is decided upon removal of the foot at the transmetatarsal site is done with

less prospect of subsequent higher amputations than was formerly the case. A careful appraisal of the circulation—methods of which are outlined on page 184, will aid greatly in coming to the proper conclusion concerning the need for amputation. Consideration is also given to the fact that the occlusive vascular disease is not confined to the legs but that the vessels of the heart, brain and kidneys have not escaped. Despite these considerations, with the skill of the surgeon, the advances in anesthesiology, and the newer drug therapies, these patients with widespread vascular disease do wonderfully well when subjected to surgery.

The indications for amputation are

1 Extensive gangrene with no improvement under conservative treatment and in a limb which is extremely impoverished of circulation.

2 Deep extensive and extending infection, and especially with an extensive osteomyelitis which is intractable to more conservative measures. A phalanx may be safely removed if the osteomyelitis is limited to a phalangeal bone.

3 Intractable pain with evidences of extreme grades of organic vascular occlusion—great care being taken not to be mistaken by a peripheral neuritis.

SITE OF AMPUTATION The level at which the amputation will be done is decided upon after a careful appraisal of the local circulation. The site selected should be high enough to be in a relatively well vascularized zone. If in the process of removing a limb the surgeon finds more extensive occlusive disease and less bleeding than he thinks might promise good post operative progress a higher site is immediately selected. In general, it is wise, in case of doubt to select the higher of two contemplated sites. Roentgen ray films may show a marked degree of arterial obstruction just above the knee. The amputation in such a case would be above the obstruction unless the evidences of an efficient collateral circulation were marked.

Anesthetic The choice of anesthetic is made by a competent anesthetist. Generally, spinal anesthesia is used for amputations. However, if there is an extreme degree of infection and necrosis and the patient shows marked evidences of a toxemia, the circulation of the limb is entirely obliterated by placing a tourniquet above the knee sufficiently tight to stop the arterial circulation, and the limb is refrigerated by packing it in ice to a point several inches above the tourniquet.³⁴ After several days, with the pronounced clinical improvement that is usual, the leg is amputated above the level of the tourniquet. With refrigeration no other anesthetic agent is used. In properly selected cases we have found the foregoing procedure to be an excellent one. Ordinarily the procedure of amputation causes little difficulty in maintaining control of the diabetes but when necessary the same measures are used as are employed with other surgical procedures as outlined on page 221.

V. Renal Disorders and Diabetes

Two renal disorders—*intercapillary glomerulosclerosis*, frequently referred to as Kimmelstiel Wilson's disease, and *pyelonephritis*—deserve special consideration because of the high incidence with which each is associated with diabetes. From the pathologist's point of view a third renal disorder—*glycogen nephrosis*—might be added. It is recognized only at autopsy by the presence of glycogen in the renal tubules and its presence bears a direct relationship to the lack of control of the hyperglycemia and glycosuria immediately preceding death. Glycogen nephrosis is of no known clinical significance except as a manifestation frequently associated with glycosuria.

Intercapillary Glomerulosclerosis. The increasing incidence of intercapillary glomerulosclerosis and the unfavorable prognosis it carries, when associated with diabetes, make this complication one of the most serious of the chronic complications. The disorder is not confined to diabetic patients but it is only in such patients that it occurs in an advanced form—doubtless because of the accelerating influence untreated diabetes exerts on the progress of degenerative disorders.

The association of intercapillary glomerulosclerosis with diabetes was recognized in 1936.¹³ Its increasing incidence has been attributed to the increased longevity of diabetic patients. Time will probably show that other factors are at work and possibly some feature or features of present day therapy for diabetes will play a part.

Intercapillary glomerulosclerosis is identified by the presence of deposits of hyaline masses in the central portions of the glomerular nodules (Fig. 9). Pathologists are not agreed about the source of the hyalin. An increasing number believe that the deposits are made in the capillary wall and not a sclerosis and hyalinization of the interstitial tissue as postulated by Kimmelstiel and Wilson. These changes have been observed in 18 to 63 per cent of diabetics coming to autopsy.¹⁴ Lukens¹ observed identical changes in the kidney of a dog kept diabetic for five years, after injections of crude extract of anterior pituitary glands.

The clinical manifestations originally reported upon were diabetes, albuminuria and edema. We have observed patients who fulfilled these criteria and in whom the disease ran a benign chronic course for many years. Albuminuria is the first indication of this complication. It tends to be intermittent at first as does edema—the second manifestation of intercapillary glomerulosclerosis. The degrees of involvement and the progressive tendencies are variable. All gradations of this complication are seen from the initial mild form to the advanced and malignant stage with full development of the nephrotic manifestations and with a life expectancy measured in months instead of years. In such cases we find *diabetes of long duration, retinal hemorrhages, edema of the extremities (or generalized), elevated*

arterial blood pressure, albuminuria, hyaline casts and red blood cells in the urine, hypoproteinemia, mild to moderate degrees of anemia and varying degrees of renal insufficiency

Intercapillary glomerulosclerosis occurs about twice as frequently in males as in females. It is most frequent in the third and fourth decades of life, is rarely seen in the second decade, and the onset decreases in frequency in those over forty years of age. In our patients having this complication, almost without exception, a history of poor control of the diabetes was secured. This is what one might expect when it is realized that no young diabetic escapes degenerative arterial disease if the diabetes is poorly controlled.

Prevention and Treatment Prophylactic and therapeutic measures are directed toward improving the patient's general clinical condition and are as follows: 1 *Control of the diabetes*. This is accomplished as indicated in Chapter XIII with the following modifications:

2 *Diet*. If there is no elevation of the blood urea nitrogen values (above 15 mg/100 cc) a liberal protein intake—up to 140 gm daily—is allowed to compensate for the loss of protein in the urine and in the attempt to replenish depleted protein stores. With urea retention the amount of protein is set at approximately 0.33 gm per pound of the standard body weight plus an amount approximately equal to that of the protein lost in the urine daily. Liberal allowance of carbohydrate, 275 to 335 gm daily, will aid in sparing kidney function. The total calories are calculated as for uncomplicated diabetes (p. 105). This diet will permit a low fat content which is desirable in any complication of diabetes in which degenerative changes in the arteries are prominent. The restriction of the salt intake to a minimum is highly desirable in the presence of edema but this restriction is cautioned against as the edema disappears in those cases in which the blood urea value exceeds normal. It is a simple matter to precipitate clinical uremia if this precaution is not heeded.

Hematinics are worth a trial. At best they are relatively ineffective and if the red blood cells are below 3,000,000 per cu mm a transfusion of whole blood, 500 cc, is given twice per week, until values closely approximating normal are reached.

Standard measures of coping with myocardial decompensation are used when indicated. *Diuretics* may be helpful but should be used cautiously if red blood cells are present in the urine in appreciable numbers.

Pyelonephritis. *Pyelonephritis is a common and dangerous complication of diabetes.* Diabetic patients, and especially diabetic women, are predisposed to infections in the urinary tract. Bowen and Kutzman¹⁸ found normal urinary tracts in only 7 of 84 unselected diabetic women. Pyelonephritis is four and one half times more common as a cause of death among diabetic than it is among nondiabetic patients,¹⁹ and of 307 deaths of diabetic patients it was the sixth commonest cause. Pyelonephritis was

the cause of 21 of these deaths.²⁰ A peculiar form of pyelonephritis—a necrotizing renal papillitis—is associated mostly with diabetes. A specific total necrosis of the renal pyramids occurs with, or without, abscess formation, and involvement of both kidneys is frequent. This serious complication occurred in 25 per cent of the cases of acute pyelonephritis and accounted for the most severe forms of the disease.²¹

A sugar laden urine is probably a better medium for organisms than urine containing no sugar. This feature and the higher frequency of bladder catheterization in diabetic subjects who have been in coma combine to increase the likelihood of pyelonephritis in these patients. Also ptosis of the kidneys, particularly on the right side, which follows the rapid loss of weight, so common in these patients, predisposes to kinking of the ureters and hence to infection. These features are apt to play a part no matter how the infection reaches the kidney—whether it be by the hematogenous or retrograde routes or invasive extension from adjacent infections.

Clinically, this complication in the typical case is characterized by the sudden onset of recurring attacks of fever, chills and backache. The urine sediment contains pus and myriads of organisms, and albumin is present.

The studies recommended in such a case comprise, first and most important, the identification of the organism by culture of the urine and the determination of its sensitivity to the various antibiotic agents. Though the colon bacillus is the most common offender this is not an adequate reason for neglecting to determine, with certainty, what organism, or organisms, are responsible. Ten cases of infections of the urinary tract in which neomycin was the only antibiotic agent to which the infecting organism was sensitive illustrate the need for highly specialized selective study and therapy.²²

The predisposition of diabetic patients to tuberculous infections is well known. The importance of identifying a renal tuberculosis while the infection is confined to one kidney is obvious.

Second, the appraisal of physical abnormalities by a urologist: this will comprise a phenolsulfonphthalein excretion test, a pyelogram—the dye being administered intravenously—and if found essential to establish the diagnosis a retrograde pyelogram is recommended.

The treatment for pyelonephritis should be prompt and conservatively aggressive. The diabetes is controlled as in the case of other acute infections (see p. 213). The degree of glycosuria is reduced in some cases by sugar consuming organisms in the urinary tract. This is a minor matter.

The therapy against the infection will be dictated by the type of organism and to which of the remedial agents it is sensitive. In the event sulfonamides are used, as is frequently the case, it is important that at least one specimen of urine per twenty four hours should be alkaline in reaction and at least 1500 cc. of urine should be excreted in this period. It is easier to secure one alkaline specimen by giving a single large dose of bicar-

bonate of soda daily than it is to keep the urine alkaline by giving multiple smaller doses. Gantrisin has gained popularity for its effect in sterilizing the urinary tract of gram negative organisms and the absence of renal complications attending its use.

Surgical measures that are indicated should be carried out without fail if the patient's clinical condition permits. The diabetes is not a deterrent to such corrective measures.

VI Ocular Lesions

Ocular changes attributable to diabetes have a degenerative basis and as might be expected patients with degenerative ocular changes present a



Fig. 24 Diabetic retinitis. Note the deep round hemorrhagic areas, the waxy exudates and decreased caliber of the arterioles.

high incidence of arterial disease—hypertension and diseases of the coronary and peripheral arteries, chronic renal disease and hypercholesterolemia. These ocular lesions have a definite and direct relationship to the duration of the diabetes and to its poor control. Sixty per cent of patients having diabetes for more than ten years show retinal hemorrhages (Waite and Beetham). Poor control of the diabetes is not always evident, however, as some patients exhibit advanced degenerative changes and yet have a mild diabetes that has not been appreciably out of hand.

The retinal abnormalities are the most frequent of the serious ocular complications. They comprise

A Vascular Changes 1 Deep, rounded punctate hemorrhages—the

most distinctive diabetic earmark in the retina (Fig 24) They are venous in origin and are not necessarily related to arterial hypertension

2 Superficial hemorrhages which tend to be flame shaped They occur in the nerve fiber layer and are of arterial origin and are related to the degree of arterial hypertension and, in at least some cases, to capillary fragility

3 Engorgement of the retinal veins

4 Narrowing of the arterioles with evidences of sclerosis, and microaneurysms of the capillaries

B Exudates 1 Waxy exudates, which appear to be the result of hyalinization of the deep retinal hemorrhages

2 Cotton wool exudates

3 Lipid deposits

C Proliferative Changes *Retinitis Proliferans* In this abnormality there is a laying down of new tissues most probably in the attempt to correct previous damage As a result dense white areas of new tissue with newly formed blood vessels are to be seen and most frequently in the region of the macula Vision is impaired up to complete blindness depending on the areas involved Contraction of the scar tissue may cause separation of the retina Also, spontaneous hemorrhage may precipitate a hemorrhagic glaucoma

Other Ocular Complications of Diabetes These abnormalities do not assume the same degree of widespread clinical importance as retinitis does but are nevertheless, not infrequently encountered in diabetic patients

disorder

2 Corneal wrinkling demonstrable with a slit lamp and a corneal microscope

3 Transitory changes in refraction occurring for a short period after a hyperglycemia is corrected (see p 167)

4 Argyll Robertson pupil—this abnormality in non syphilitic diabetic subjects is a manifestation of neuropathic changes (see p 215)

5 Xanthelasma Patches of lipid deposits on the eyelids are an innocent complication of diabetes although they are not distinctive of this disease

6 Tobacco amblyopia has been observed by one of us, in two diabetic patients recently Improvement followed the withdrawal of tobacco and the control of a mild diabetes in each instance

Treatment for ocular complications of diabetes includes

1 Control of the diabetes

2 The use of a diet liberal in protein not less than 100 gm for the male nor less than 90 gm for the female diabetic and including liberal amounts

of carbohydrate (250 to 335 gm) and small amounts of fat—below 75 gm daily

3 Ascorbic acid, 200 mg daily, with rutin, 20 to 200 mg three times daily according to the degree of capillary fragility as determined by the Gothlin index test are worthy of a trial in cases of retinal hemorrhages

4 Cataracts are treated as in the nondiabetic subject

5 Transitory refractive errors due to a reduction of hyperglycemia are managed as outlined on page 167

6 Neurologic changes involving the eyes as part of a diabetic neuropathy are treated vigorously and in the same manner as other neurologic abnormalities (see p 207)

7 Xanthelasmic patches ordinarily should not be interfered with. If removed they almost invariably recur

VII *Neurologic Disturbances Complicating Diabetes*

Neurologic disturbances are among the most common complications of diabetes. Collens and coworkers²³ found these abnormalities in 93 per cent of all their diabetic patients. The cause or causes of these disorders are not entirely clear but accumulated evidences preponderantly indicate that disturbances in nutrition which accompany loss of weight in the presence of a long standing and poorly controlled diabetes are the usual precipitating factors. Although uncontrolled diabetes and loss of weight are usual forerunners of these disturbances, this is not always so. In fact, findings typical of the milder forms of so called diabetic neuropathy have been observed in patients before the diabetes developed. Also, patients who have not lost weight and whose diabetes has been under excellent control for long periods may experience a mildly progressive neuropathy indistinguishable from that ordinarily accepted as diabetic in origin. It would appear that there is an underlying disturbance which tends to be intensified by poor control of the diabetes and loss of weight but that these features are not essential to its development. It is true, however, that this type of neuropathy is seen for the most part but not exclusively in diabetic patients. Acute infections and vitamin deficiencies may play a part but it appears that these, with the possible exception of vitamin B₁₂ deficiency, are modifying circumstances rather than essential features. The neurologic abnormalities are degenerative in nature and it is not surprising that the other major degenerative disorders are frequently found in varying grades of development in subjects with neurologic disturbances. We refer especially to diabetic retinitis, disease of the coronary arteries, the kidneys and peripheral vascular disease. The various neurologic disorders associated with diabetes are, in all likelihood, part of the same process but observed at different phases and under different circumstances they present features so variable that their separation into several categories is not surprising.

The detection of a diabetic neuropathy in its early stages is of utmost

importance for this purpose studies of the vibratory sense are particularly valuable. Disturbances in the vibration sense are recognized clinically by (a) decreased acuity or a complete inability to detect the vibrations of a tuning fork and (b) increased perception time. Barach²⁴ and Collens²⁵ have attracted attention to the value of this examination. We can support their claims and emphasize that the common error of attributing symptoms of neurologic origin to disturbances in circulation can be eliminated if proper investigation of each possibility is carried out. We consider the neurologic survey to be one of the most important in appraising the clinical status of the diabetic patient.

For the detection of an impaired vibration sense a tuning fork of an aluminum alloy with a frequency of 128 (Fig. 25) serves admirably. The detection of the vibration and the prompt recognition of its cessation—

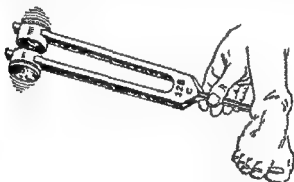


Fig. 25. A tuning fork as used in the detection of disturbances of vibration sense.

the patient's eyes being closed—is evidence of a normal vibratory sense. The handle of the vibrating tuning fork is applied to bony prominences—the sternum, radius, ulna, crest of the ilium, sacrum, tibia, the malleoli and the metatarsophalangeal prominences—in determining the patient's vibration sense. Studies involving upper extremities are done largely to acquaint the patient with the procedure. Impaired vibration sense in the upper extremity occurs but not nearly as frequently nor to as great a degree as is observed in the legs and feet.

The degenerative changes which account for the blocking of the transmission of the vibratory impulses occur in the posterior columns of the spinal cord and in the peripheral nerves. In diabetes the latter is predominant.

The vibration sense normally is less acute in older age groups, it is variable under normal circumstances, and findings indistinguishable from those found in diabetes are observed in patients with tabes dorsalis and with primary or pernicious anemia.

For practical purposes the following classification of the diabetic neuropathies has proved to be satisfactory

Chronic Neuropathies. A The *early or mild* and often ill defined form of diabetic neuropathy—the most common form—is gradual in onset and the symptoms, most frequently encountered and associated with loss of weight and uncontrolled diabetes for long periods, are vague pains aches, shooting pains, *cramps*, numbness, *tingling and burning*, lightning stinging or needling sensations, stiffness and formication, most frequently occurring in the legs and feet but occurring infrequently in the upper extremities and in the trunk *These symptoms tend to be worse at night and upon exposure to cold* The increasing intensity of these symptoms at night provides a clue in differentiating neurologic disturbances from a circulatory insufficiency Tendon reflexes are frequently impaired or absent Tenderness of the calf muscles is common and some impairment in the vibratory sense is usual in the legs and feet in this relatively early phase

This disorder may remain relatively stationary for long periods in some patients but characteristically it subsides readily with the control of the diabetes and with appropriate supplementary therapy

B The *moderately severe* stage of diabetic neuropathy is characterized by greater disturbances in the tendon reflexes, and in the vibratory sense The symptoms have been present for a prolonged period and areas of cutaneous paresthesia are often detectable We include also in this group those cases with abnormalities of the autonomic nervous system which respond satisfactorily to therapy in contrast to those which do not and which are classified in the severe or refractory group Falling in this moderately severe group are some cases of intermittent nocturnal diarrhea, or intermittent diarrhea and constipation, stubborn constipation of relatively recent onset, delayed emptying of the stomach, impotence, vasomotor instability causing giddiness on rising from the recumbent to the erect position due to orthostatic hypotension and absent sense of bladder filling These patients tend to be underweight and indeed it is quite likely that malnutrition plays a contributory part in the production and maintenance of this clinical state

Involvement of the autonomic nervous system is detected in patients having disturbances of the gastro intestinal and the genito urinary tracts The development of obstinate constipation or, as occurs in some instances, diarrhea which is especially troublesome at night, is not infrequent These two disorders sometimes alternate in a single patient The absence of free hydrochloric acid from the gastric secretions is a prevalent but not an essential finding Incontinence of feces has been noted Epigastric pain, indistinguishable from the gastric crises of tabes, is occasionally encountered Roentgenologic studies indicate disturbed motility in the gastro intestinal tract with, in some cases, a scattered barium pattern as seen in severe deficiency states Unlike the steatorrhea of pancreatic insufficiency, the diarrhea

of diabetic neuropathy is not influenced by the oral administration of pancreatic extracts

Involvement of the peripheral autonomic nerves leads to reduction or elimination of perspiration in the involved areas reduced vasomotor and pilomotor function and to dependent edema secondary to the altered permeability of the capillaries. Reduced functioning of the sebaceous glands may account for the atrophic and shiny changes which the skin of the extremities undergoes.

Orthostatic hypotension occasionally occurs as a result of neurocirculatory abnormalities in patients exhibiting characteristics of diabetic neuropathy. Dizziness, weakness on physical exertion and, in the more severe grades of the disorder, syncope occur in association with the decrease in blood pressure which follows the change from the supine to the standing position.

Disturbances in the genito-urinary tract identifiable with diabetic neuropathies include disturbances in sphincter control due to degenerative changes in the pudendal nerves permitting dribbling paralysis of the bladder with the 'cord bladder' syndrome—painless distention of the bladder with retention of urine, an impaired sense of bladder filling and a predisposition to infection in the genito-urinary tract. Sexual impotence is a common complication. This may exist with or without a loss of libido. Loss of ejaculatory power may exist without loss of potentia but a combination of these disorders is the rule, with atony of the bladder an additional but less frequent complication.

C. *The late, severe and relatively refractory neuropathies in the diabetic patient* are uncommon in contrast with the frequent occurrence of the milder forms. The most frequent complaints when peripheral nerves are involved are loss of weight, general weakness, disturbed sensation in feet varying from numbness, tingling, pins and needles sensation, a feeling that 'his feet do not belong to him,' to complete loss of sensation with painless ulcerations. Foot or wrist drop is an uncommon feature but unsteadiness of gait is not infrequent.

Involvement of the peripheral nerves and the fasciculi proprii of the spinal cord causes disturbances in the tendon reflexes. There may be complete absence of all reflexes but *diminished or absent Achilles reflexes* are especially frequent, as is a depression of the peripheral superficial sensibilities. *Reduced pupillary responses* to light even to the degree observed in the Argyll Robertson pupil have been observed.

Cases of *neurotropic feet* in which there is complete loss of sensation and great destruction of bone (Fig. 26) are uncommon although we have seen five such cases in the past year. Chronic ulcerations of the feet may be mistaken for diabetic gangrene on the basis of arteriosclerosis of the tarsals but in the cases we have seen the tips of the toes have been warm and there has been excellent pulsation of the peripheral arteries of the feet. Destruc-

tion of bone and the extrusion of bony fragments through a sinus at the base of an ulcer may occur. Shortening and stubbiness of the foot develops as a result of marked destruction of bone.

There are evidences that, in some cases, this destruction of bone is due to a secondary infectious process but in others the disorder appears to be on a purely neurotrophic basis.

In cases of extreme degree irreparable organic changes in the nervous system have been noted. The following case report is illustrative.

J. C. a male pharmacist aged forty three years when admitted to the Pennsylvania Hospital in 1949, gave a history of having had diabetes mellitus for fourteen years. During that period the diabetes was under irregular control, with 35 to 50 units of insulin daily.

About two years previously there was swelling of the right foot. At first this swelling disappeared on bed rest but later it became constant. Four months before admission he experienced numbness of the feet and of the fingertips. About the same time edema of the left foot and an ulcer on the right great toe appeared. Later an ulcer appeared on the left great toe and another under the proximal end of the left metatarsal bones.

He gave no family history of diabetes. He had had chronic intermittent diarrhea with "milky fatty stools" of three years' duration, anemia with pallor, and dizziness of similar duration, left abductens nerve weakness and diplopia for six weeks and morning nausea, relieved by food, of seven months' duration. The patient's weight had been from 132 to 134 pounds (60 to 61 kg.) for the preceding eight months.

The physical examination revealed a systolic blood pressure of 178 mm Hg with a diastolic pressure of 120 mm, normal pupillary reactions to light, arteriovenous nicking of the retinal vessels, arteriolar sclerosis, round hemorrhages and waxy yellow exudates on ophthalmoscopy, generalized pallor of the skin and mucous membranes, the liver was not palpable, 4 plus pitting edema of the right foot, ankle and lower leg, 1 plus edema of the left foot and ankle, with a marked increase in

absence of touch, pain, vibration and position sensation in the feet and ankles bilaterally, hypalgesia over the dorsolateral surface of both legs, loss of vibration sense in the tips of all fingers of the right hand and in the fourth and fifth finger tips of the left hand, tenderness over the course of the femoral and peroneal nerves and absent patellar and Achilles tendon reflexes bilaterally, and a positive Romberg sign was elicited.

serum albumin of 3.5 gm. and a cholesterol value of 310 mg. Phenolsulfonphthalein excretion tests showed that 5 to 10 per cent of the dye was excreted in twenty minutes with a total two-hour excretion of 30 to 35 per cent. There was a marked excess of fat in the stools. Gastric secretion contained less than normal amounts of free hydrochloric acid prior to the administration of histamine. Serologic tests on

ed but incomplete destruction of the (Fig. 26). There was considerable soft tissue swelling and periosteal proliferation along the lateral margins of the fourth and fifth metatarsal bones. In the left foot only two indistinct radiolucent areas in the cuboid bone and periosteal proliferation along the fifth metatarsal

were observed. Films of the hands were negative except for stress of bone destruction at the distal end of the middle phalanx of each middle finger.

During the patient's course in the hospital, his diabetes was controlled by 42 units of protamine zinc insulin and 11 units of regular insulin given separately before breakfast and a 2800-cal per diet containing 175 gm of protein, 300 gm of carbohydrate and 100 gm of fat in three equal feedings and a bedtime nourishment.

He was given transfusions of whole blood, dilute hydrochloric acid by mouth a course of penicillin therapy, supplementary vitamins, and boric acid solution soaks and furacin ointment applied locally to the pedal ulcerations.

The diarrhea promptly ceased and the stools became normal. The hemoglobin concentration rose to 12 gm per 100 cc and the red cell count to 4.0 million per cu mm. The blood urea nitrogen concentration remained elevated but was not made

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	52
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Fig. 26. Extensive destruction of bone as seen in a case of neurotrophic foot in a diabetic patient (1) (-).

perished. The ulcerations healed slowly and incompletely. There was no change in the neurologic abnormalities or in the appearance of the bones of the feet on roentgen ray films.

This patient had diabetes mellitus, diabetic retinopathy neuropathy with neurotrophic ulcerations and bone lesions of the feet and intercapillary glomerulosclerosis (Kimmelstiel-Wilson's disease).

Subsequent to discharge a prolonged course of vitamin D₃ therapy was without striking benefit. Although after two years the degenerative disorders do not appear to have progressed unfavorably.

Treatment for Diabetic Neuropathy Vitamin B₁₂ has been, in our experience, the most promptly effective measure in correcting these neuropathic disorders. It is given intramuscularly in doses of 30 micrograms daily for three to five days and thereafter once per week has been adequate. The relief from night pains and from the swaying or giddiness on walking; has been so prompt as to leave no uncertainty about the specific relief which this drug provides. Also, a return of the vibratory sense is noted withi

few days and a more gradual correction of impotence has been observed. Relief also follows the administration of large doses of vitamin B complex but it is achieved at a considerably slower rate.

Control of the diabetes and especially if the diet is low in calories and unless fortified with vitamins may increase the intensity of the neurologic manifestations. This is avoided by giving a diet of sufficiently high caloric value to prevent a reduction in weight for the time being, by controlling the diabetes with insulin and by employing vitamin B₁₂ therapy.

Acute Peripheral Neuritis This distressing complication is infrequent in contrast to the common chronic neuropathies. Sciatica serves to illustrate this group. The onset of this true form of peripheral neuritis is usually rapid with severe pain throughout the distribution of the involved nerve, intensified by motion and with exquisite tenderness on pressure over the nerve, and with tender muscles. Involvement of the muscular function varies from a mild degree of weakness to actual paralysis as seen in foot or wrist drop. Atrophic changes occur in prolonged cases. Absent tendon reflexes in the involved zones, e.g., the Achilles reflex in cases of sciatica, is characteristic. Poisoning with heavy metals, thiamine deficiency, infections, exposure to cold and pressure on or invasion of, nerve trunks by neoplastic growths, are causes of peripheral neuritis and are to be considered in addition to the diabetes. When directly attributable to the disturbed physiology associated with diabetes the duration of attacks varies from three to twelve weeks.

Treatment Therapy for acute peripheral neuritis in the diabetic is identical with that for the nondiabetic with the added features (a) *prompt control of the diabetes*, and (b) the prevention of a loss in weight. The reduction of body weight tends to intensify the symptoms and great care should be taken to maintain the existing weight, even in the obese patient, until the neuritis is corrected.

Thiamine hydrochloride, 50 mg., is administered intramuscularly daily until relief is secured, and vitamin B₁₂, 30 micrograms, is given intramuscularly daily for three to five days and thereafter once weekly.

Other features of treatment are *rest in bed*, and infra red heat treatments over the involved areas for at least one half hour several times daily.

Acetylsalicylic acid, 0.6 gm. (10 gr.) three times during the day, and an *enteric-coated tablet of sodium salicylate*, 0.6 gm. (10 gr.) before retiring are recommended. When the pain is severe *codeine sulfate*, 0.03 gm. (0.5 gr.), may be used to supplement the salicylates.

VIII Tuberculosis

Diabetic patients are especially susceptible to tuberculous infections. Pulmonary tuberculosis was about twice as common in 3106 diabetics as in a comparable nondiabetic group.²⁶ It was three times as common in those taking more than 40 units of insulin daily as in those taking less or

no insulin, and tuberculosis was about twice as common in diabetic patients who were below the standard weight in contrast with those above standard weight. Attacks of diabetic coma predispose to the development of pulmonary tuberculosis.

TABLE 31

THE SIMPLICITY OF THE CONTROL OF A SEVERE DIABETIC DURING A FAMILIAL PHASE OF AN ACTIVE PULMONARY TUBERCULOSIS

A B Weight 59 kg Height 176 Cm

Diagnosis Diabetes Mellitus Active Pulmonary Tuberculosis

DATE (Y-M)	GLUCOSE (Mg)	URINARY GLUCOSE ACCORDING TO				INSULIN (units)	DIET			
		8 A.M.	3 P.M.	8 P.M.	9 P.M.		1	2	3	Cal
		g	g	g	g		g	g	g	g
Dec 10	308	4+	4+	3+	3+	90 I.P. I 40 C. (before)	100	122	2-3	500
11		4+	3+	3+	3+	85 I.P. I 40 C. (before)				
12	272					90 I.P. I 50 C. (before) 8 C. (after) or 10 C. (after)				
Data and Insulin Levels are based upon average and given at 4 hr. intervals										
		8 A.M.	3 P.M.	8 P.M.	9 P.M.	URINARY GLUCOSE				
		g	g	g	g	8 A.M.	3 P.M.	8 P.M.	9 P.M.	
13		4+	4+	3+	3+	30	30	30	30	100 122 2-3 500
14		30	30	30	30	30	30	30	30	
15		30	30	30	30	30	30	30	30	
16		30	30	30	30	30	30	30	30	
17		30	30	30	30	30	30	30	30	
18		30	30	30	30	30	30	30	30	
19		30	30	30	30	30	30	30	30	
20		30	30	30	30	30	30	30	30	
21	139	30	30	30	30	30	30	30	30	

Note: Urinary glucose figures represent results of tests for anhydrous F. Z. = Protein no data.

Prevention. Patients are cautioned against contact with individuals known to have tuberculosis. It is highly desirable for every diabetic, and especially if he is underweight, to have a roentgen ray film of his chest once yearly. Good hygienic measures aid in preventing tuberculous infection.

- 15 Kimmelstiel P., and Wilson C. *Am J Path.*, **12** 83, 1936
- 16 Mann G. V. *et al* *Am J Med.*, **7**:3 1949
- 17 Lukens, F. D. W., and Hoban, F. C. *Arch. Path.*, **41**:19 1946
- 18 Bowen H. D. and Kutzman N. *Ann Int Med.*, **17** 127 1942.
- 19 Rollins, S. L., and Tucker A. W. *New England J Med.*, **231** 865, 1944
- 20 Robbins S. L. *Bull. New England J Center* **10**:78 1948
- 21 Duncan G. C. Wolgam t J R., Clancy C. F., and Ledleman, R. *J A.M.A.*, **145**:75, 1941
- 22 Wente J. H. and Latham W. P. *New England J Med* **212**:399 and 429 1935.
- 23 Collins W. S., *et al* *Am J M Sc.*, **219**:182, 1950
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CHAPTER XVI

Acute Complications of Diabetes

Diabetic patients are exposed to the same acute complications as non diabetics but there are certain abnormalities to which they have a special predilection (see Table 32). Of the latter, *diabetic coma* (discussed in Chap XVII), *myocardial infarction* and *acute infections* complicating occlusive vascular disease in the extremities are the most common. Infectious proc-

TABLE 32

THE RELATIVE INCIDENCE OF ACUTE COMPLICATIONS IN 514 CONSECUTIVE DIABETIC PATIENTS ADMITTED TO THE PUBLIC WARD OF THE PENNSYLVANIA HOSPITAL

Skin Infections	67
Respiratory Tract Infections	65
Urinary Tract Infections	56
Cardiac Failure	46
Gangrene of Lower Extremity	43
Myocardial Infarction	38
Gynecologic Conditions	33
Fractures	28
Cerebral Vascular Disease	21
Diabetic Ketosis	14
Cancer of Digestive Tract	12
Peritonitis	11
Cholecystitis	8
Osteomyelitis	6
Cancer of Respiratory Tract	6
Embolism	6
Hyperthyroidism	5
Miscellaneous	171
Total	633

esses are among the most common acute complications of diabetes and it is not an unimportant fact that in most instances these acute episodes are superimposed on chronic degenerative disorders, notably arterial disease. This circumstance tends to modify the treatment as well as the prognosis. Myocardial infarction is an acute and serious complication which occurs, in a large part, as the result of chronic degenerative changes in the coronary arteries. The clinical aspects of chronic and acute coronary artery

insufficiency including coronary occlusion, and the myocardial infarction which results, are dealt with on page 181.

ACUTE INFECTIONS

Acute infections are the most common of the acute complications. They impair the effectiveness of insulin and tend to precipitate a high degree of hyperglycemia and diabetic ketosis progressing to coma with great speed, that is, in a matter of hours. The effect of fever alone, and fever plus infection on the duration and degree of the blood sugar lowering effect of insulin in contrast with the effect when no fever nor infection nor leukocytosis are present is diagrammatically depicted in Figure 27. For these

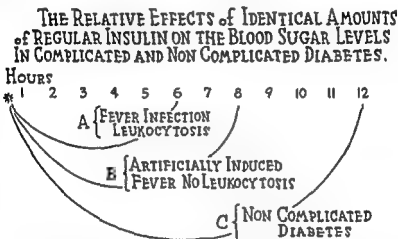


Fig 27 The differences in the blood sugar lowering effect and the duration of the effectiveness of identical doses of regular insulin under normal and abnormal circumstances are diagrammatically presented (Duncan Carey and Hudson Medical Clinics of N. A. Nov. 1919)

reasons and the fact that recovery from infections is retarded if the diabetes is not adequately controlled special attention toward the prevention of infection and a special alertness when infection is already present yield high clinical dividends.

Diabetes is more difficult to control during acute infections and it is for this reason that changes in the distribution of the diet and insulin are usually made—changes which permit more certain and prompt control of a diabetes which under the abiding circumstances is likely to get out of hand with remarkable rapidity.

Patients with uncontrolled diabetes have a subnormal resistance to infectious organisms, especially to the tubercle bacillus and the *Staphylococcus aureus*.

All of the reasons why acute infections affect the diabetes so unfavorably

ably are not known but we do know that infections which increase the need for insulin most markedly are those causing *fever* and *leukocytosis*, and that the behavior of the diabetes is frequently a *reliable index*, favorable or unfavorable, of the trend of an infectious process. The duration of insulin action is reduced as is its degree of action by acute infections accompanied by fever and leukocytosis. Infections not causing fever have little effect on the insulin need and those which cause no leukocytosis cause relatively little increase in the need for insulin. Viral infections and tuberculosis are examples of the latter. If secondary pyogenic organisms get a foothold, as in the case of an acute sinusitis complicating a simple coryza of viral origin or a mixed infection in a case of pulmonary tuberculosis, a change in the need for insulin is likely to be prompt.

Increases in tissue metabolism, derangement of enzymatic processes and increased proteolytic activities in the blood in patients having a fever and leukocytosis may explain the behavior of the need for insulin but, until the problem is clearer and until more specific means of attacking it are available, we are obliged to continue with the excellent therapeutic means at hand, even if they may appear cumbersome.

It will be concluded from the foregoing remarks that patients who have mild diabetes and ordinarily not needing insulin will almost always require insulin if an acute infection is contracted. There are a few patients who have no detectable evidences of diabetes under normal circumstances but who have manifest diabetes during the course of an acute infection, notably infections due to the *Staphylococcus aureus* and especially carbuncles.

Prevention: Preventive measures comprise immunization when practicable, control of the diabetes, an adequate diet, hygienic care of the skin and special care of the feet, as has been stressed already.

Treatment for Acute Infections—General Considerations: The features in therapy for diabetic patients suffering from acute infections are

A. Cognizance of the effect which infections exert on the diabetes and on the need for insulin.

B. Specific measures directed toward eradicating the infection—drainage, antibiotic or sulfa therapy, and the occasional use of antitoxin.

C. Insulin therapy—who should receive insulin, the brand of insulin, the amounts and the distribution.

D. Diet therapy—alterations in diet and in its distribution.

E. Special measures—surgery, roentgen ray irradiation, intravenous therapies.

Specific Considerations: A. The effect which infections exert on the diabetes has been discussed at the outset of this section, page 213.

B. Specific measures to be taken to eradicate infection are of great importance. The high degree of specificity with which antibiotic drugs overcome bacterial infection makes the early identification of the offending

organism or organisms and their respective sensitivities to the various antibiotic agents of great importance. *Best results will follow if material for a culture is secured at once before any antibiotic agent is given.* The material for culture growth may be from a carbuncle, furuncle, abscess, discharging sinus, an ulcer, the urine, the blood, the spinal fluid, etc.

This procedure need not delay therapy. As soon as the culture material is secured the antibiotic agent which seems most likely to be effective is given. Too often we find carbuncles which have been doing badly and threatening life, only to find that the offending organism is resistant to the antibiotic—practically always penicillin—that the patient has been receiving. The broader is the scope of the bacteriology laboratory in detecting the specific sensitivities the more often prompt cures will result.

Other specific measures should not be overlooked, e.g., adequate drainage in cases of pent up purulent material.

INSULIN THERAPY. Insulin is given to every patient, no matter what is the degree of severity of his diabetes, if his fasting blood sugar level exceeds 120 mg per 100 cc or if the postprandial value exceeds 160 mg per 100 cc.

We use regular insulin exclusively during the course of moderately severe and severe infections. In many cases, however, the disturbance is so slight that small to moderate increases in the amount of long acting insulin given will suffice without disturbing the usual routine. For the more severe infections regular insulin only is used. It is not used in combination with a slowly acting insulin because the latter does not exert a uniform effect throughout the twenty four hours.

The action of regular insulin is prompt and the fact that its action is of short duration makes it a simple weapon to manipulate when both the blood sugar level and the insulin requirement may be subject to rapid alterations.

The following method of distributing the insulin has been employed at the Pennsylvania Hospital for the past seventeen years with favorable results. During the course of moderately severe infections the insulin is given in four divided doses at evenly spaced intervals. The diet is similarly divided so that the patient receives the same amount of carbohydrate, fat and protein after each injection of insulin. It is convenient to give meals and insulin at 6 A.M., 12 noon, 6 P.M. and 12 midnight. This program permits the uniform control of the blood sugar level during the most severe complications. Changes in the dosage of insulin are regulated according to the amount of sugar found in the urine, which is collected before each nourishment and by the level of the blood sugar (see Table 33).

Occasionally, in cases of very severe infections and in which very large amounts of insulin, several hundreds of units daily, are given, it has been a temporary expedient to divide the insulin into six doses and the diet into

six equal nourishments, both given at four hour intervals. As the critical phase passes, the injection of insulin and a nourishment are given every six hours.

The regulation of the insulin dosage in the case of a patient taking 80 units of insulin prior to admission for treatment for a carbuncle is illustrated in Table 33.

In the unusual case when meals and insulin are given at four hour intervals, collections of urine are made for the same periods, and likewise when meals and insulin are given every six hours, the urine is collected each six hour period. The bladder is emptied before each feeding and the degree of glycosuria is determined.

The degree of, or the absence of, glycosuria is a suitable guide in changing the dosage of insulin (see Table 33), but occasional blood sugar determinations are of value. Of great value is the testing of the plasma for acetone. The patient is in no danger from ketosis if there is no detectable acetone in the plasma or serum. For the technic of performing this test, see

TABLE 33
AN ILLUSTRATIVE GUIDE TO INSULIN THERAPY IN THE CASE OF
AN ACUTE INFECTION

Time	12 M	6 P M	12 M	6 A M	12 M	6 P M	12 M	6 A M	12 M
Glycosuria	4+	4+	3+	2+	0	1+	0	0	0
Acetonuria	2+	1+	1+	0	0	0	0	0	0
Plasma Acetone	0	0	0	0	0	0	0	0	0
Blood Sugar mg /%	320							135	
Insulin	25	40	50	40	35	35	30	25	25

page 69. If the patient's condition is not progressing favorably and the infection is of a serious nature and there is acetone in the urine, a test for acetone in the plasma is advisable at least twice daily. The presence or absence of acetone in the urine ordinarily is a good guide but if the reaction is 4 plus it is important to know to what extent the acetone bodies are accumulating in the blood.

The change from the pre-complication insulin regimen is illustrated in Table 34. This program is illustrative only. It provides a simple means of crudely estimating a safe initial program of insulin therapy, following which the amounts of insulin given are altered as indicated according to the degree of, or absence of, glycosuria as illustrated in Table 34. The initial dose of insulin for the patient having a mild diabetes can safely be 12 units. For those receiving insulin routinely the initial dose will not be excessive if it equals one quarter of the routine dose plus a moderate increase. The determination of the initial dose is illustrated for varying de-

degrees of insulin need, in Table 31. The insulin is increased at each injection until the diabetes is brought under relatively good control. It is well to maintain a fairly firm rein on the diabetes. To do this when the time to reduce the insulin dosage arrives it is preferable to reduce and *not to omit* a dose. Nothing will upset diabetic control more quickly than omitting a dose of insulin when a reduction in the amount given is all that is needed. As the infection subsides the insulin is reduced steadily to prevent hypoglycemic reactions. The need for great reductions is often necessary following the prompt correction of an infection. In such cases there is little danger in making big reductions—as long as heavy reactions for glycosuria are not present—until the pre-complication dosage of insulin is nearly approximated.

The pre-complication regimen is resumed after one or two days have elapsed without fever. This can be done abruptly, e.g., 20 units of regular

TABLE 31
A GUIDE IN CHANGING THE RESPECTIVE INSULIN PROGRAMS IN THE EVENT OF ACUTE COMPLICATIONS

PRIOR TO COMPLICATION	During Complication— THE INITIAL DOSE— REGULAR INSULIN
(1) No insulin	III
(2) Single doses of 30 units or less of P. Z. insulin Glolan or NPH insulin	15
(3) Combined insulin therapies totaling 80 units	25
(4) Combined insulin therapies—total 100 units	40
(5) Combined insulin therapies—total 130 units	50

Note: The initial dose is one-quarter of the former daily dose plus a moderate increase. Subsequent doses will be adjusted according to the degree of glycosuria in each succeeding six-hour urine fraction.

insulin given at six hour intervals (total for twenty four hours—80 units) is replaced by 60 units of protamine zinc insulin and 20 units of regular insulin injected separately.

DIET THERAPY As has been indicated in the foregoing paragraphs, the diet is divided into four equal feedings during acute illnesses—except in rare cases when six equal feedings, one every four hours—are given.

The diet requires some modification from the usual form. It is important to maintain an adequate protein allowance—a minimum of 0.5 gm. per pound of the normal body weight. Liquids fortified with concentrated protein foods are desirable if the usual protein foods are unpalatable. Convalescence is speeded by giving more liberal allowances of protein—up to 0.66 gm. per pound of body weight. This protein quota is especially desirable in dealing with prolonged infections or open wounds such as ulcers from which much protein is lost. Liquid nourishment may be all that the acutely ill patient can take and this should consist largely of fruit juices, skimmed milk, cream, gruels and ginger ale with glucose.

Diet XII
Liquid Diet—Four Equal Meals
 (Protein 110 gm., Fat 65 gm. Carb 250 gm.—2000 Calories)

NO EXCHANGES	FOOD EXCHANGE	LIST NO	SAMPLE MENU	HOUSEHOLD MEAS	WT GM	P	F	C	CAL.
6 00 A.M.									
1	Bread	1	Oatmeal in	½ c	20	11	—	15	68
1	Milk	1	Milk whole	1 c	210	8	10	12	170
2	Meat	5	Lactose or sugar or dextrin	2 tbsp	20	—	—	20	80
1½	Fruit	3	Eggs oodled	2	—	14	10	—	145
			Pineapple juice	½ c	120	—	—	15	60
			Total			24	20	62	524
12 00 NOON (Repeat at 6 00 P.M. with suitable exchanges)									
			Soup (thin with broth)						
2	Meat	5	Meat puree	2 oz	60	14	6	—	110
1	Bread	4	Potato mashed	1½ c	100	2	—	15	68
1	Vegetable	2B	Peas puree	½ c	100	2	—	7	36
1½	Fruit	3	Grapefruit juice	¼ c	150	—	—	15	60
1	Milk	1	Milk whole	1 c	210	8	10	12	170
			Lactose or sugar or dextrin	4 tsp	15	—	—	15	60
			Total			26	16	64	504
12 00 MIDNIGHT									
2½	Milk	1	Milk drink	1 pt	480	16	—	24	160
1	Milk	1	Milk, skim	1 tbsp	12	2	—	1	24
1	Meat	5	Milk, skim powder	2	—	14	10	—	116
			Eggs	1	10	—	—	10	40
1	Fat	6	Lactose or sugar or dextrin	1 th-p	30	—	5	—	45
2	Fruit	3	Light cream	2 th-p	120	—	—	20	80
			Grape juice	½ c		—	—	58	495
			Total			32	15	88	707
			Day's Total			108	67	248	2027

This liquid diet is designed for patients with acute complications and who are unable to eat regular food. The division into four equal meals, one every six hours in conjunction with four doses of regular insulin facilitates the control of the diabetes during emergency periods (see p. 217).

DIET VIII
Hot or Dry Fat in Egg at Meals
(Protein 110 gm Fat 65 gm Carb 250 gm—2000 Calories)

NO EXCHANGES	PER 100 EXCHANGE	LIST NO	SAMPLE MEAL	MEAL HOLD MEAL	WT GR	P	F	C	CAL
6:00 A.M.									
2	Bread	1	Bread	1 M	25	2	—	15	110
2	Milk	5	Buttermilk	1/2 C	100	2	—	15	110
1 1/2	Milk	1	Milk	1 C	210	8	10	—	116
1	Fat	1	Milk skim powder	1 tsp	12	—	—	12	70
1 1/2	Fruit	3	Butter	1 tsp	5	—	—	1	21
			Banana	1/4 can	75	3	—	—	15
			Total			28	15	15	160
12:00 Noon (labeled at 6:00 P.M. with usual exchanges)									
2	Milk	5	Hot roast beef	2 oz	60	11	6	—	110
2	Bread	1	Bread	1/2 C	25	2	—	15	68
1	Vegetable	2A	Lettuce and tomato	100	90	2	—	—	—
1	Vegetable	2B	Carrots	100	100	2	—	7	36
1	Milk	1	Milk skim	1/2 C	210	8	—	12	80
2	Fat	6	Butter	2 tsp	10	—	10	—	60
1 1/2	Fruit	3	Pear	1 med	150	—	—	15	60
			Total			20	16	61	512
12:00 MIDNIGHT									
1 1/2	Milk	1	Milk skim	1 C	210	8	—	12	80
2	Milk	5	Milk skim powder	1 tsp	12	—	—	1	21
1	Bread	1	Cottage cheese	1/2 C	90	11	10	—	116
1	Fat	6	Saltines	5	20	2	—	15	78
3	Fruit	3	Butter	1 tsp	5	—	—	—	15
			Grape juice	1/4 C	180	—	—	20	120
			Total			26	15	61	483
			Day's Total			110	62	250	1998

This diet, equally divided into four nourishments illustrates that employed for treatment during acute complications when a dose of regular insulin is given at six hour intervals (see p 217)

A sample diet prescription is as follows

Protein	110 gm
Carbohydrate	250 gm.
Fat	50 gm
Total calories	2000

This diet is presented in menu form as a liquid diet (Diet VII) and a diet of normal foods (Diet XIII). In each instance the diet is divided into four equal meals suitable for use in most cases of acute complications. Following the recovery from the acute complication the pre-complication diet is resumed simultaneously with resumption of the former plan of insulin therapy.

PARENTERAL NOURISHMENT When a patient cannot take feedings by mouth or by gavage, an intravenous program of feeding is used being patterned on the six hour schedule outlined above. No method in present use can supply adequate nutrition by this route, and caution must be exercised to use it no longer than necessity dictates and to prevent the excessive administration of sodium chloride.

We have found the basic formula, for parenteral feedings as recommended by the National Research Council to be eminently satisfactory.

To meet the requirements for the nutrition of a patient who will be unable to take any food or fluids for some days and therefore should receive a nutrient which will provide an adequate amount of some protein substitute.

Water	3 000 cc
Casein hydrolysate	100 Gm.
Glucose	200 Gm
Salt	10 Gm.

This will require two liters of five per cent casein hydrolysate five per cent glucose solution and one liter of 10 per cent glucose solution a total of 3 000 cc. Since the casein hydrolysate is neutralized it will contain 5 Gm. of salt per liter or 10 Gm. in two liters. Other convenient formulae can be devised by which the volume can be kept below 3 000 cc. *

An intravenous infusion of 750 cc. is started every six hours and regular insulin is injected subcutaneously as each infusion is begun.

The quantity of fluids given is adjusted to promote and maintain normal hydration. Mild degrees of glycosuria are permitted as a safeguard against a hypoglycemia but sufficient amounts of insulin and carbohydrate are given to prevent appreciable degrees of acetonuria. Blood sugar values are likely to be misleading while glucose is being administered by vein.

The dosage of insulin is regulated in such cases also according to the degree of glycosuria. For an unconscious or incontinent patient an indwelling catheter is introduced into the bladder, under appropriate precautions in order that the samples of urine may be secured. Gantrisin is employed

in doses of 1 gm four times daily, as a prophylactic agent against infection in the urinary tract while the catheter is in place.

The methods of therapy for diabetic patients having acute complications and surgery at the Pennsylvania Hospital have been reported and evaluated in some detail by Alexander, Loomis and Lee.² Considerable portions of the article which deal with surgery and diabetes are presented verbatim with the authors' consent.

SURGERY AND DIABETES

Insulin therapy has made it possible to give diabetic patients all of the benefits of surgery with prospects of results closely approaching those achieved with nondiabetic subjects. For the relative frequency of surgical conditions in the acute complications see Table 35.

TABLE 35

THE RELATIVE INCIDENCE OF SURGICAL COMPLICATIONS IN 514 CONSECUTIVE DIABETIC PATIENTS ADMITTED TO THE PUBLIC WARD OF THE PENNSYLVANIA HOSPITAL BECAUSE OF ACUTE COMPLICATIONS

Anjulation of Extremity	41
Gynecologic Operations	33
Ligation of Vein	32
Intra-abdominal Surgery	29
Incision and Drainage	21
Sympathectomy	14
Operations on the Larynx	10
Normal Delivery of Child	8
Radiocal Mastectomy	4
Intralumbar Operations	3
Thyroidectomy	3
Miscellaneous	3
Total	275

The diabetes is controlled prior to elective operations but in emergencies diabetes is not a contraindication to surgical procedures provided a moderate or severe degree of ketosis is not present, i.e., a 2 plus or greater reaction for acetone in the plasma or a CO_2 combining power of the plasma below 35 volumes per cent.

Procedure of Therapy. Our procedure in preparing these patients for operation has been as follows:

1 *Elective Surgery.* Patients undergoing elective surgery are kept on their usual routine of therapy until the day of operation.

2 *Non-elective, Non-emergency Surgery.* In non-elective surgery when a delay of two or three days is permissible, the diabetes is controlled using the four equal meals, one every six hours, and each preceded by a dose of regular insulin. This is identical with the plan of therapy for acute infections (see p. 217).

3 Emergency Surgery When immediate surgery is necessary and (a) the diabetes is not complicated by ketosis, no delay is indicated, but (b) when the patient has ketosis with a 2 to 3 plus reaction for acetone in the plasma or a CO_2 combining power below 35 volumes per cent, a delay of four to six hours will be adequate, with liberal doses of insulin given subcutaneously and glucose and normal saline given intravenously, to restore the carbohydrate metabolism and water balance sufficiently to proceed with the operation (c) Patients in diabetic coma should not be subjected to surgery beyond minor remedial measures, e.g., myringotomy for the drainage of an abscess, the opening of an airway, the arrest of hemorrhage, or other measures to forestall an immediate disaster

The Day of Operation Procedures for this day are modified by the urgency and nature of the operation, the severity of the diabetes, the clinical condition of the patient, the anesthesia, the necessity in some cases for an empty stomach, and the prospective ability of the patient to take food orally after the operation

In dealing with the diabetes there are two main objectives (1) Avoid ketosis, and (2) avoid hypoglycemic reactions

Management of the diabetes is integrated with the other needs of the patient as indicated by our usual program, which is as follows

1 Nourishment, Fluids and Sodium Chloride The six hour schedule of giving nourishment is adhered to The nourishment before operation is given as 1 liter of 5 or 10 per cent solution of glucose Following operation the basic plan is to give 750 cc of a 5 or 10 per cent solution of glucose intravenously, slowly, in each six hour period A new bottle is started every six hours Every third bottle (or 1000 cc as the case may be) should be given as a 5 per cent solution of glucose in normal saline If nourishment is given in this manner for more than one or two days, casein hydrolysate is added—the equivalent of 25 gm of protein per day

On some occasions more fluids are indicated, in which case 1 liter is given in place of a 750 cc administration (see Fig 29) Contrariwise, in cases of surgical shock with anuria and a lower nephron nephrosis resulting, the amount of fluid would be reduced to approximately 1200 cc daily until urine is secreted We have had no occasion to resort to this measure for a diabetic patient

2 Insulin Ordinarily one-quarter of the previous day's total dose of insulin is given prior to the preoperative administration of glucose This is not a fixed rule It may be advisable to give less if there is any fear of hypoglycemia, if the operation is prolonged the risk of a hypoglycemia can be eliminated by giving glucose intravenously during the latter stages of the operation

Postoperatively the amounts of insulin, a dose every six hours, are regulated according to the degree of glycosuria Mild degrees of glycosuria are preferable during the first two or three postoperative days

Simple operative procedures—the ligation of veins, incisions and drainage, and dental extractions—and, indeed, many amputations may be performed without any change in the four meal schedule, the operation being simply inserted between feedings.

Four illustrative plans of therapy in operative cases are presented in Figure 28. It will be observed that nourishments are given at 9 A.M., 3 P.M., 9 P.M.,

DIAGRAMS to ILLUSTRATE PLANS for MANAGEMENT of DIABETES on OPERATIVE DAY

For Incision and Drainage Vein Ligation and Similar "Minor" Procedures

	3AM	6AM	9AM	12M	3PM	6PM	9PM	12M
FEEDINGS								
IV GLUCOSE								
INSULIN								
OPERATION								

For Amputation Setting of Fractures

	3AM	6AM	9AM	12M	3PM	6PM	9PM	12M
FEEDINGS								
IV GLUCOSE								
INSULIN								
OPERATION								

For Amputation TRANSURETHRAL PROSTATECTOMY

	3AM	6AM	9AM	12M	3PM	6PM	9PM	12M
FEEDINGS								
IV GLUCOSE								
INSULIN								
OPERATION								

GASTRECTOMY and THYROIDECTOMY and CHOLECYSTECTOMY

	3AM	6AM	9AM	12M	3PM	6PM	9PM	12M
FEEDINGS								
IV GLUCOSE								
INSULIN								
OPERATION								

Fig. 28. Four plans of therapy for diabetic patients subjected to surgery of varying degrees of complexity are depicted diagrammatically. (After Alexander J. D., Loomis, A. H. and Lee C. T., Jr. Medical Clinics of North America, Sept., 1919.)

9 P.M. and 3 A.M. This timing is a matter of convenience and is obviously quite as suitable if a 12 noon, 6 P.M., 12 midnight, and 6 A.M. schedule is selected.

The normal distribution of meals—usually three meals and a bedtime nourishment—and insulin are resumed when the patient is able and can take regular food. The transition from the six hour schedule to the normal

regimen is performed in the same manner as that following an acute infection (see p 217).

An illustrative operative case reported by Alexander and his co workers² is presented as follows:

A fifty eight year-old diabetic Negress, E P, was admitted on February 26, 1948 with a body temperature of 101° F and symptoms and signs which strongly suggested a diagnosis of acute cholecystitis. Operation was deferred until the acute process had subsided.

A cholecystectomy was performed on March 9, 1948, under nitrous oxide-oxygen ether anesthesia. The pathologist's diagnosis was chronic cholecystitis and cholelithiasis. A Wangenstein drainage was maintained for twenty four hours after operation. Fever was present for three days postoperatively with a maximum of 101.2° F but convalescence was otherwise uneventful and the patient was discharged March 20, 1948, on the eleventh postoperative day.

The diabetes was treated on admission by means of a 2100 calorie liquid diet divided into four equal feedings with 14 units of regular insulin before each feeding. Prior to this illness the insulin requirement was 28 units a day. Glycosuria was eliminated by the second day in the hospital. On the day of operation, as shown in

	3/9/48				3/10/48				3/11/48
	3AM	9AM	3PM	9PM	3AM	9AM	3PM	9PM	3AM
ORAL FEEDINGS									
IV GLUCOSE SOL		++++	++++	+++	+++	+++	+++		
INSULIN									
URINE SUGAR	0	0	3+	2+	1+	1+	1+	0	0
OPERATION									

DIAGRAMMATIC REPRESENTATION of ILLUSTRATIVE
OPERATIVE CASE (CHOLECYSTECTOMY)

Fig 29 The plan of medical therapy for a diabetic patient (E P) undergoing a cholecystectomy is depicted (Alexander, Loomis and Lee Medical Clinics of North America, Sept, 1949)

Figure
was g
same
5 per
operat

normal saline was used. Reactions for glycosuria remained 2 plus or less and those for acetone remained negative in all specimens.

By 3 PM March 10, liquid feedings could again be tolerated and a four meal diet similar to the preoperative diet was ordered. Regular insulin was given, as usual, before each feeding. Return to a three meal diet and long acting insulin was accomplished prior to discharge from the hospital.

This case history illustrates the general management of a diabetic patient requiring major surgery. It demonstrates the preoperative four meal schedule used as the basic pattern during the operative and postoperative periods. When it was impossible to use oral feedings, glucose solutions were given

intravenously, each infusion being started at the time when the meal would have been served. Regular insulin administered subcutaneously was used throughout the critical period and always at the beginning of a feeding or infusion. This case is unusual in that the dose of insulin did not need to be altered during the entire operative period. Also, the amount of fluid given was greater than would ordinarily be required.

Choice of Anesthesia. It is preferable to have a qualified anesthetist, who is familiar with the patient, to make the choice of the anesthetic. When practical, local or regional anesthesia is desired. For amputations spinal anesthesia is our choice except in the occasional case in which the limb has been refrigerated (see p. 196). In this event no further anesthesia is necessary. For general anesthesia induction with gas-oxygen and continued with ether is eminently satisfactory. Nitrous oxide is the general anesthetic of choice for short operations and when good relaxation of the abdominal muscles is not a requisite.

Every effort is made to avoid anoxia. Morphine, if used, is given in minimal doses. Chloroform and ethyl chloride are contraindicated for diabetic patients.

REFERENCES

1. Duncan G. G., Carey L. S., and Haison M. T. *M. Clin. North America* (Nov.) 1919 p. 1337.
2. *National Research Council in Convalescence and Rehabilitation* Report No. 1 (Feb.) 1944.
3. Alexander J. B., Loomis, A. H., and Lee C. T., Jr. *M. Clin. North America* (Sept.) 1919 p. 1413.

CHAPTER XVII

Diabetic Coma

Introduction The pathologic physiology of diabetic coma has been dealt with in Chapter VIII. As an introduction to the practical features it suffices to say that (a) Diabetic coma is one of the greatest of medical emergencies (b) It is preventable (c) It does not develop while the diabetes is under good control (d) It is recognizable and may be readily corrected in its early stages (e) Deaths from diabetic coma have been reduced dramatically but they still occur because of ignorance, delay and neglect (f) Fatalities may occur from hypopotassemia appearing as a complication of therapy for diabetic coma (g) Hypopotassemia* is readily detected by electrocardiographic studies and can be prevented or corrected by the oral administration of potassium chloride.

The prompt detection of hypopotassemia and its correction is of new and important interest. At the outset of therapy for diabetic coma, as a rule, there is a hyperpotassemia as indicated in the electrocardiographic record in Figure 30, but as therapy is carried out several processes which tend to reduce the concentration of potassium in the circulation are in operation. These are: the dilution factor, the excretion of potassium in the urine, the loss by vomiting, inadequate intake, the utilization of this electrolyte in the laying down of glycogen and of protein and other factors not clearly understood.

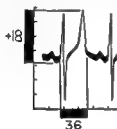
Potassium chloride can be given routinely as indicated in the outline of therapy. There need be no concern of this therapy doing harm if urine is being excreted freely. Anuria tends to prevent hypopotassemia. The routine administration of potassium chloride should be omitted if the patient is anuric. This is recommended for two reasons: (1) because a hyperpotassemia may be precipitated and (2) because there is not likely to be a need for it during this period.

An excellent review of the present status of potassium therapy has been published by Elkinton and Tarant¹.

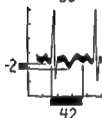
Nature of Diabetic Coma and Its Diagnosis Diabetic ketosis progresses until the patient is in a state of coma, occurs when the utilization

* Potassium is present in normal serum in concentrations of 3.8 to 4.3 mEq/L. (14.8 to 16.8 mg./100 ml.)

of carbohydrate is reduced to a degree which causes an increase of great magnitude in the metabolism of fat. As a result, acetone bodies (acetone, diacetic acid and beta hydroxybutyric acid) are produced at a rate which exceeds the ability of the body to complete their oxidation and the excess, in the early stages, is excreted in the urine. As this process progresses 1 plus reactions for acetone in the urine are replaced by 2 plus, 3 plus, and finally 4 plus reactions. The kidneys, and to a minor extent the lungs, can carry off, for variable periods, the excess acetone bodies from the blood but, bar-



SERUM K = 77
R-R (SEC) = 64
CALC QT = 32



SERUM K = 31
R-R (SEC) = 56
CALC QT = 296

Hypokalemia

QT interval normal

Lower tracing—serum K 31 mEq/L
(12 mg/100 mL)

T wave inverted

QT interval prolonged

ring relief, finally acetone production exceeds the functional capacity of the excretory mechanisms and acetone bodies accumulate in the blood. At first, this stage is detectable by the appearance of traces of acetone in the blood plasma but, if not corrected, 2 plus, 3 plus, and finally 4 plus qualitative reactions for plasma acetone are observed. Usually, it is not until 4 plus reactions for acetone in the urine are observed for variable periods that amounts of acetone increase in the plasma to a sufficient concentration to be detected by the usual tests employed. Hence, in general, a 3 or 4 plus reaction for acetone in the plasma indicates a much more advanced degree of ketosis than do similar reactions obtained on examination of the urine.

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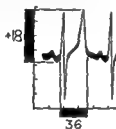
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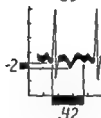
Nature of Diabetic Coma and Its Diagnosis. Diabetic ketosis progressing until the patient is in a state of coma, occurs when the utilization

* Potassium is present in normal serum in concentrations of 3.8 to 4.3 mEq/L. (14.8 to 16.8 mg/100 ml.)

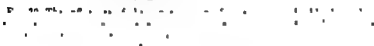
of carbohydrate is reduced to a degree which causes an increase of great magnitude in the metabolism of fat. As a result, acetone bodies (acetone, diacetic acid and beta hydroxybutyric acid) are produced at a rate which exceeds the ability of the body to complete their oxidation and the excess, in the early stages, is excreted in the urine. As this process progresses 1 plus reactions for acetone in the urine are replaced by 2 plus, 3 plus, and finally 4 plus reactions. The kidneys, and to a minor extent the lungs, can carry off, for variable periods, the excess acetone bodies from the blood but, har-



SERUM K = 7.7
R-R (SEC) = 64
CALC QT = 32



SERUM K = 3.1
R-R (SEC) = 56
CALC QT = 296



T wave—increased amplitude with a narrow base
QT interval normal

Hypokalemia

Lower tracing—serum K 3.1 mEq/L
(12 mg/100 ml.)
T wave inverted
QT interval prolonged

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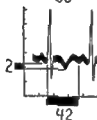
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* Potassium is present in normal serum in concentrations of 3.8 to 4.3 mEq/L (148 to 168 mg/100 ml)

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SERUM K = 7.7
R-R (SEC) = 64
CALC QT = 32



SERUM K = 3.1
R-R (SEC) = 56
CALC QT = 296

12 10 8 6 4 2 0 2 4 6 8 10 12

T wave—increased amplitude with a narrow base
QT interval normal

Hypokalaemia

Lower tracing—serum K, 3.1 mEq/L
(12 mg/100 ml.)
T wave inverted
QT interval prolonged

ring relief finally acetone production exceeds the functional capacity of the excretory mechanisms and acetone bodies accumulate in the blood. At first, this stage is detectable by the appearance of traces of acetone in the blood plasma but, if not corrected, 1 plus, 2 plus and finally 4 plus qualitative reactions for plasma acetone are observed. Usually, it is not until 4 plus reactions for acetone in the urine are observed for variable periods that amounts of acetone increase in the plasma to a sufficient concentration to be detected by the usual tests employed. Hence, in general, a 3 or 4 plus reaction for acetone in the plasma indicates a much more advanced degree of ketosis than do similar reactions obtained on examination of the urine.

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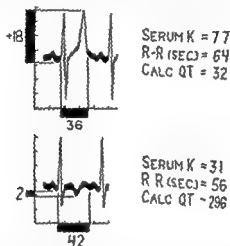


Fig. 30 The influence of the concentration of potassium in the blood on *ecg* cardiographic records are illustrated in precordial lead CR₁. (After *Waller et al.*)

Hyperkalemia Upper tracing—serum K 7.7 mEq/L (130 mg/100 ml.)
T wave—increased amplitude with a narrow base
QT interval normal.

Hypokalemia Lower tracing—serum K 3.1 mEq/L (12 mg/100 ml.)
T wave inverted
(QT interval prolonged)

ring relief finally acetone production exceeds the functional capacity of the excretory mechanisms and acetone bodies accumulate in the blood. At first, this stage is detectable by the appearance of traces of acetone in the blood plasma but, if not corrected, 2 plus, 3 plus, and finally 4 plus qualitative reactions for plasma acetone are observed. Usually, a next still 4 plus reactions for acetone in the urine are observed for variable periods that a "one increase in the plasma" to a sufficient concentration to employed. Hence, in from 2 3 or 4 plus

The diabetic patient having 4 plus reactions for glycosuria and acetoneuria, and a 4 plus reaction for plasma acetone fulfills the chemical criteria necessary to make the diagnosis of diabetic coma. The diagnosis can be made at the bedside. Urine for testing is obtained by catheter if necessary and 10 cc. of oxalated blood allowed to stand for a few minutes will provide plasma or serum, of which only one drop is needed in the test for acetone (see p. 69).

Excessive production of ketones provides the clue to the diagnosis and the early detection of this clue is of extraordinary importance. The simplicity of the tests for acetone in the plasma puts a precise and valuable diagnostic measure in the hands of every physician. The diagnosis can be established without elaborate equipment or technical assistance and—of most importance—therapy can be started at once. It is practicable then, even in remote places, to give a patient in diabetic coma the opportunities of recovery closely approaching those enjoyed by patients in large cities with nearby hospital facilities. In case of the latter group their chances of recovery from diabetic coma are also greatly enhanced if the diagnosis is made in the home and not delayed until the patient is admitted to the hospital. We know of a patient in whose case the diagnosis was made and 100 units of insulin and 3 ounces of well salted broth were given within thirty minutes of the time the physician saw the patient. This illustrates what can be the next great advance in the management of diabetic coma—immediate diagnosis with insulin and sodium chloride administration begun in all cases preliminary to moving the patient to the hospital.

Prior to and in the early stages of ketosis important disturbances in the patient's fluid and electrolyte balances have been taking place, notably the increased hyperglycemia with its diuretic effect, the loss in the urine of large quantities of sugar and of base, especially sodium and to a smaller degree but nevertheless of great importance, potassium. All have a bearing on the clinical state of the patient and on the therapy necessary. These later considerations account for the intense dehydration, hemoconcentration, increased specific gravity of the whole blood, low, and at times imperceptible blood pressure, vascular collapse with evidences of the resulting renal incompetence as indicated in the gravely ill patient by oliguria with albumin and granular casts, or in some instances by anuria with the development of the uremic state, if correction is delayed. If the shocklike state prevails for many hours, changes in the renal tubules characteristic of a lower nephron nephrosis may occur. In these rare cases the excessive administration of fluids is fraught with great danger.

Second only in importance to an early diagnosis and insulin therapy are the halting and correction of these secondary and dangerous processes. Administration of salty broth, orally, as soon as the diagnosis is made will often turn the tide favorably and in some cases will be life saving. Most medical writings deal almost exclusively with diagnosis and treatment of

coma in hospitalized patients. This communication stresses also what can be done in the field so to speak, or, as it were, at the front line before evacuating the patient to the hospital.

Precipitating Causes of Diabetic Coma Any factor or factors which increase total tissue metabolism with one exception—physical exercise—tend to intensify the diabetes and as a result increase the need for insulin. Illustrations of this effect are observed in cases of thyrotoxicosis, pregnancy, febrile disturbances and gain in body weight. A diagrammatic illustration of the reduction in the effectiveness of insulin during acute complications is presented in Figure 27.

The unfavorable influence of increasing total metabolism alone or when combined with other features which predispose to and cause diabetic coma may precipitate a clinical emergency with great rapidity. The pregnant and the thyrotoxic diabetic patients who develop acute infections illustrate this group, as do the neglected obese diabetic patients who acquire staphylococcal skin infections, notably carbuncles. Also, the patient who disregards—by ignorance or indifference—dietary restrictions and overeats, with the result that the diabetes is out of control, is predisposed to develop ketosis when a precipitating factor makes its appearance. He is a candidate for a rapidly developing ketosis in the event of infections even of a minor nature, gastro intestinal disturbances (vomiting or diarrhea), surgical complications and the omission of insulin. It is remarkable how frequently the diabetic patient, because of anorexia during an acute complication, omits insulin. This may be done with or without the advice of a physician. In such cases the anorexia is frequently due to ketosis in its early stages and all that remains to speed the quickest possible development of coma is the withdrawal of insulin therapy. The anorectic diabetic patient is a potential emergency at all times but when the anorexia is associated with some other disorder, be it an upper respiratory tract infection, gastro intestinal upset or one of the possible multitude of complications, the emergency exists and careful clinical evaluation and therapy are necessary if needless risk is to be avoided. Such patients who exhibit strongly positive reactions for glycosuria and acetonuria and whose plasmas give a 2 plus or 1 plus reaction for acetone are in the pre coma state.

The anorexia of the diabetic patient suffering from an acute clinical condition is intensified by nausea and, with the onset of vomiting and its unfavorable influence on the fluid balance and chloride depletion, the dehydration and vascular collapse in these patients are quickened.

Sodium chloride administered as salty broth in the anorectic phase may halt and will certainly postpone the downward progress. We have repeatedly observed that this simple measure has alleviated nausea, and vomiting often ceases when salty broth is ingested. Failing an early diagnosis or early treatment or both, the ketosis gains headway slowly—several days to weeks—in the neglected diabetic without acute complications, but the ketosis de-

velops very rapidly—a matter of hours—in the presence of acute infection and toxemia

Prevention Diabetic coma is preventable but to achieve this goal patients must be trained thoroughly concerning (a) the factors which precipitate coma, (b) the speed with which coma may develop and (c) the manner in which the early symptoms are manifested. Also, we must make earlier diagnoses, provide adequate therapy and safeguard against over treatment if this complication is to be prevented, and corrected with minimum risk if it is already established

Patients should be aware of the benign course which controlled diabetes pursues and the upheaval that can come with great rapidity with an acute infection. It is remarkable how many patients test the urine regularly for sugar only until they feel badly and, by discontinuing tests with the onset of a complication, deprive themselves of the only real clue that they understand, namely, strongly positive reactions for glycosuria. Following in rapid succession come the anorexia, nausea and often vomiting. The speed with which these patients may pass into the danger zone cannot be over emphasized.

With adequate training diabetic patients make provision for *testing the urine* in the event of illness and they will always regard *loss of appetite* with or without *nausea* in the presence of *strong reactions for glycosuria* as danger signals concerning the correction of which their physician should be consulted. Also, the patient should know that in the anorexic phase insulin must not be omitted if strongly positive reactions for glycosuria are present. The pre-coma state should be suspected under these circumstances. In case this suspicion is confirmed by a 4 plus reaction for glycosuria and acetonuria and a 1 or 2 plus reaction for plasma acetone, small frequently administered doses (every four hours) of regular insulin are indicated. The amounts are regulated according to the changes in the degree of glycosuria. In these instances the administration of salty broth by mouth will usually alleviate the nausea and permit frequent administration of carbohydrate by mouth which, with the accompanying insulin therapy, will quickly correct the early ketosis. *Too little attention has been given in medical literature to the value of sodium chloride in dealing with the pre coma state*

In the event that the acute complication which is precipitating the ketosis is not correctable promptly—within a matter of hours—the danger of ketosis can be reduced and the control of the diabetes can be more exactly regulated by prescribing the diet in four equal feedings—one every six hours—and regular insulin—one fourth of the former total insulin dosage plus a modest increase—before each feeding making adjustments according to the effect on the glycosuria in the respective six hour fractions. We have used and advocated this principle of treatment for many years. It has received widespread acceptance. Illustrative insulin regimens are presented in Table 34, page 217

A liquid diet divided into four equal feedings which has been found to be satisfactory is presented in Diet VII. When regular foods are tolerated a diet as illustrated in Diet VIII, may be employed until the routine diet and insulin may be resumed after the acute complication has subsided.

Treatment. Therapy is directed at the fundamental faults by giving insulin frequently and in adequate amounts, by restoring fluids and electrolytes until normal values prevail, and by providing adequate carbohydrate to permit a reduction in fat metabolism and to replenish depleted glycogen stores. Other, but secondary, therapeutic measures are included in the following outline of treatment for diabetic coma employed at the Pennsylvania Hospital.

Outline of Treatment for Diabetic Coma. The working diagnosis of diabetic coma is made when 4 plus glycosuria, 4 plus acetonuria, and 4 plus plasma acetone are found in the case of an acutely ill patient. When these findings are present:

I Begin treatment immediately

Insulin (regular)—40 units intravenously*

60 units subcutaneously

Fluids and Chlorides—2000 cc normal saline are given intravenously (give rapidly—15 to 20 cc per minute—if systolic blood pressure is below 90 mm Hg)†

II Studies—Secure immediately

(1) Blood for sugar content, acetone bodies, hematocrit, CO_2 combining power, specific gravity (whole blood), and urea determinations

(2) Urine for culture and routine complete analysis

III The Director of the Medical Division or, failing to reach him, a senior assistant will be notified promptly by the medical resident of the admission of a patient in diabetic coma. The resident will also alert the Laboratory for emergency studies. Also, arrangement for full time service of a resident and nurse should be made until the patient's life is out of danger.

IV Secure urine at two hour intervals‡ for sugar and acetone determinations until the ketosis is corrected.

V Secure blood specimens at four hour intervals, day and night, for acetone, CO_2 and sugar and specific gravity (whole blood) until

* With the exception of this initial dose all insulin is administered subcutaneously.

† Heat should not be applied to patients in diabetic coma as the peripheral vasodilatation which it causes may intensify the shocklike state. Normal room temperatures are quite satisfactory.

‡ A retention catheter may be used for this purpose when necessary. Utmost care

in twenty four hours. Immediately prior to removal of catheter a urine specimen for culture is obtained.

the patient is conscious and retaining nourishment by mouth. Subsequent studies as conditions indicate.

- VI Secure an electrocardiogram as early as is practicable and repeat at four hour intervals for twenty four hours. More frequent tracings are indicated to guide therapy in cases of hypopotassemia.
- VII Treatment During Critical Phase Subsequent to the Preliminary Measures Outlined in I

Immediately upon receiving confirmative reports on the blood sugar value and the plasma CO_2 combining power, or within one hour of making the diagnosis whichever is earlier, begin

Insulin (regular) 50 units subcutaneously at one-half hour intervals until an appreciable reduction of the plasma acetone or increase in the CO_2 combining power is noted. Increases above these amounts will rarely be necessary, but if no decrease in plasma acetone or increase in CO_2 combining power of the blood plasma has occurred after six hours* of therapy each succeeding dose may be increased by 25 units until such changes are noted. Dangers of a rapidly developing hypoglycemia will be avoided by giving glucose (1 liter of 5 per cent solution) intravenously after six hours of therapy (see Par V) or carbohydrates orally, if practicable.

VIII When to Reduce Insulin

An appreciable reduction of the plasma acetone and an appreciable increase of the CO_2 combining power of the blood plasma coincide with a lessening of the resistance to insulin. Such findings should put the physician on the alert to the possibility of a rapidly developing hypoglycemia. When the clinical condition and laboratory findings indicate that the patient is showing satisfactory progress the insulin dosage schedule on an hourly and later two or three hour basis may be guided as follows:

- 4 plus glycosuria—30 units
- 3 plus glycosuria—reduce to 20 units
- 2 plus glycosuria—reduce to 10 units
- 1 plus glycosuria—omit dose
- 0 glycosuria—omit dose of insulin and give 20 gm carbohydrate

The reduction of plasma acetone to a trace or an increase of the CO_2 combining power to a value above 40 volumes per cent is, if the clinical condition of the patient permits, indication for insulin and diet at six hour intervals (see Par VIII).

IX Fluids and Salts

Loss of electrolytes and fluids to a marked degree occurs in the

* It is usual to find little change in the blood findings in the first four hours but by the end of six hours improvement should be noted unless unusual circumstances are present.

development of diabetic coma. Correction of these deficiencies at the earliest opportunity is imperative. This is done properly by the intravenous administration of physiologic saline solution, in amounts of 2000 to 3000 cc. within the first two hours of treatment. Further administration is given freely while the specific gravity of the whole blood remains above 1.055 while the hematocrit values remain above 50 per cent and the systolic blood pressure remains below 90 mm. Hg. As soon as the patient's condition permits, broths and carbohydrate containing fluids—strained cereal gruel, ginger ale (non-effervescent), sweetened tea and later fruit juices—may be given. Potassium chloride,* 1 gm. every four hours for five doses is given routinely to the adult patient after four hours of therapy provided urine is being excreted freely. Relatively smaller amounts are given to children. Accurate records of fluid intake and output are essential.

V Carbohydrate

Glucose 1000 cc. of a 5 per cent solution in normal saline, is given intravenously beginning six hours after the first dose of insulin is given if at this time liquids given orally are not retained. This is repeated in six hours if the patient is not taking or retaining nourishment by mouth.

XI Alkali

The administration of alkali usually is not necessary. However, an amount of racemic sodium lactate sufficient to raise the CO_2 combining power to a relatively innocent level—30 volumes per cent—will relieve air hunger rapidly. Larger amounts are contraindicated. The foregoing amount of alkali is permissible also for the critically ill patient having a plasma CO_2 combining power below 15 volumes per cent. A transfusion using whole blood is an efficient means of restoring both base and blood volume.

XII Gastric Lavage—Enema

The stomach should be emptied of its contents in cases of abdominal distention, abdominal pain or vomiting. Eight ounces of warm normal saline solution are left in the stomach. An enema is indicated in nearly every case of coma. It may be delayed until improvement in the patient's condition is noted.

XIII Diet

When evidences of acute ketosis have subsided, a liquid diet is allowed for twelve to twenty-four hours and thereafter a "house diet" of the same values—for example, protein 110 gm., fat 65 gm., and carbohydrate 250 gm. (2000 calories). The diet is given in

* If indications of hypopotassemia are not corrected promptly by the oral administration of potassium chloride give 100 to 500 cc. of a 1.24 per cent solution intravenously slowly until a satisfactory electrocardiographic response is observed.

four equal feedings, one every six hours; and finally, with complete recovery from the attack, the diet and insulin regimens as for the uncomplicated diabetic patient are resumed.

Case Report. The case report of a patient treated recently for diabetic coma is presented. It illustrates many of the features already touched upon in this communication and others that will be dealt with in chronological order.

E. D., a Negress, aged thirty-six years, was admitted in a profound coma to the Pennsylvania Hospital on March 4, 1919. Relatives stated that the patient was three

TABLE 37
SUMMARY OF LABORATORY DATA AND THERAPY (PATIENT E. D.)

DATE	BLOOD						URINE		
	Sugar mg / 100 cc	CO vol per cent	Acetone in plasma	Urea mg / 100 cc	Hem atocrit per cent	Sp Gr	Sugar	Acetone	Amount (cc)
3/4/19									
11 00 A M	1452	12	++++	38	51		++++	++++	300
1 00 P M	1372	16	++++		48	1 066	++++	++++	135
3 00 P M	861	18	++++	31	38	1 079	++++	++++	700
5 00 P M	831		++++		41	1 059	++++	++++	1125
7 00 P M		33	++++		32		+++	++++	775
9 00 P M	377		++++		35		+	++++	150
11 30 P M	291		++++		35		0	++++	175
First 12 hours									3360
1 30 A M	287		+++		37		0	++++	150
3 30 A M	324		++		35		+	+++	—
5 30 A M	231	49	+				0	+	—
9 00 A M	186		+	26	36		+	+	300
Second 12 hours									450
24 Hour Totals									3810

Total fluids administered: First 12 hours 8730 cc —intravenously

Second 12 hours 3900 cc —orally

Total insulin administered: First 12 hours 1350 units

Second 12 hours 400 units

months post-partum and that since the delivery and following a "cold" she had complained of excessive thirst and appetite and the frequent passing of large amounts of urine and that she had lost weight from 216 pounds to 211 pounds in this period. The family doctor had made the diagnosis of diabetes one week before her admission but his advice to seek hospital care went unheeded. The patient had no appetite for food on the day prior to admission and toward evening she had "difficulty getting enough breath." At 4 00 A M on the day of admission she was found to be unconscious and could not be aroused.

On admission a catheterized specimen of urine gave 4 plus reactions for glycosuria and acetoneuria and there was a 4 plus reaction for plasma acetone. The criteria for diabetic coma being fulfilled, insulin was given at once—50 units of regular insulin intravenously and 50 units of regular insulin subcutaneously. Also, an intravenous

infusion of normal saline was begun. Chemical studies of the initial specimen of blood revealed a blood sugar level of 14.2 mg per 100 cc and a CO_2 combining power of the plasma of 12 volumes per cent.

The physical examination revealed the profound state of coma, marked obesity, a severe degree of dehydration, and typical Kussmaul breathing also of a severe degree. The tongue was red and dry and the conjunctival reflexes were absent. The blood pressure was 95 mm Hg systolic and 50 diastolic, the pulse rate 156 and the body temperature 102° F (rectal). Otherwise the physical findings were not remarkable. The lungs were clear and there was no distention of the abdomen. Laboratory findings summarized in Table 37 show plasma sugar 14.2 mg per 100 cc, plasma acetone 4 plus, CO_2 combining power 12 volumes per cent, blood urea nitrogen 38 mg per 100 cc, glycosuria and acetonuria 4 plus, albuminuria 2 plus, and many granular casts in the urine. The leukocyte count was 17,650 per cu mm of blood. There were 5,000,000 red cells per cu mm, the hematocrit reading was 51 per cent and the specific gravity of the whole blood was 1.066.

Insulin. Insulin, with the exception of 200- and 100-unit doses administered early in the treatment, was given in doses of 50 units every half hour until the blood sugar was reduced to 377 mg per 100 cc. The totals amounted to 1350 units in the first twelve hours of therapy and 1750 units in the first twenty-four hours. This amount of insulin far exceeds the quantity usually necessary to correct ketosis. It will be observed in Table 37 that there are no evidences that excessive amounts of insulin were given nor were there, at any time, clinical signs of overdosage. It was considered of utmost importance that large amounts of insulin be given frequently with ample carbohydrate as long as 4 plus reactions for plasma acetone were found. As the concentration of plasma acetone decreases the sensitivity to insulin increases, hence a lessening of the amounts of insulin as well as a reduced frequency of administration are imperative if hypoglycemic reactions are to be prevented.

Fluids. An extreme degree of dehydration was clinically manifest, the blood pressure was 95 mm Hg systolic and 50 mm diastolic and the specific gravity of the whole blood was 1.066 (normal 1.052 to 1.058). These studies when repeated indicated that despite the administration of unusually great amounts of fluids—2700 cc of normal saline in the first two hours of therapy and 6200 cc in the first six hours—the specific gravity of the whole blood was still elevated—1.059. Nevertheless with progress being otherwise favorable the rate of the administration of fluid was sharply reduced. The total volume of fluids—normal saline, plasma and glucose in distilled water—given in the first twelve hours reached a total of 8730 cc. In the second twelve hours of treatment fluids given by mouth amounted to 3900 cc, bringing the total in the first twenty-four hours to 12,630 cc. Less fluid in this latter period might have sufficed but with a urine volume of only 450 cc, a smaller fluid intake was not justified. Also, dehydration was still manifest. The large output of urine in the first twelve hours was not attributable to excess fluid intake but rather to the diuretic influence of the hyperglycemia which prevailed. When this was alleviated the positive water balance was enhanced.

four equal feedings, one every six hours, and finally, with complete recovery from the attack, the diet and insulin regimens as for the uncomplicated diabetic patient are resumed

Case Report. The case report of a patient treated recently for diabetic coma is presented. It illustrates many of the features already touched upon in this communication and others that will be dealt with in chronological order.

E. D., a Negress aged thirty six years was admitted in a profound coma to the Pennsylvania Hospital on March 4, 1949. Relatives stated that the patient was three

TABLE 37
SUMMARY OF LABORATORY DATA AND THERAPY (PATIENT E. D.)

DATE	BLOOD						URINE		
3/4 49	Sugar mg / 100 cc	CO ₂ vol per cent	Acetone in plasma	Urea mg / 100 cc	Hem atocrit per cent	Sp Gr	Sugar	Acetone	Amount (cc)
11 00 A. M.	1452	12	++++	38	51		++++	++++	300
1 00 P. M.	1372	16	++++		48	1.066	++++	++++	150
3 00 P. M.	864	18	++++	31	38	1.059	++++	++++	700
5 00 P. M.	834		++++		41	1.059	++++	++++	1125
7 00 P. M.		33	++++		32		+++	++++	775
9 00 P. M.	377		++++		35		+	++++	150
11 30 P. M.	291		++++		35		0	++++	175
First 12 hours									3360
1 30 A. M.	287		+++		37		0	++++	150
3 30 A. M.	324		++		35		+	+++	—
5 30 A. M.	251	49	+				0	+	—
9 00 A. M.	186		+	26	36		+	+	300
Second 12 hours									450
24 Hour Totals									3810

Total fluids administered: First 12 hours 8730 cc—intravenously

Second 12 hours 3900 cc—orally

Total insulin administered: First 12 hours 1350 units

Second 12 hours 400 units

months postpartum and that since the delivery and following a cold she had complained of excessive thirst and appetite and the frequent passing of large amounts of urine and that she had lost weight from 246 pounds to 211 pounds in this period. The family doctor had made the diagnosis of diabetes one week before her admission but his advice to seek hospital care went unheeded. The patient had no appetite for food on the day prior to admission and toward evening she had difficulty getting enough breath. At 4 00 A. M. on the day of admission she was found to be unconscious and could not be aroused.

On admission a catheterized specimen of urine gave *4 plus reactions for glycosuria and acetonuria and there was a 4 plus reaction for plasma acetone*. The criteria for diabetic coma being fulfilled insulin was given at once—50 units of regular insulin intravenously and 50 units of regular insulin subcutaneously. Also, an intravenous

infusion of normal saline was begun. Chemical studies of the initial specimen of blood revealed a blood sugar level of 1452 mg per 100 cc and a CO_2 combining power of the plasma of 12 volumes per cent.

The physical examination revealed the profound state of coma, marked obesity, a severe degree of dehydration and typical Kussmaul breathing also of a severe degree. The tongue was red and dry and the conjunctival reflexes were absent. The blood pressure was 90 mm Hg systolic and 50 diastolic, the pulse rate 156 and the body temperature 102° F (rectal). Otherwise the physical findings were not remarkable. The lungs were clear and there was no distention of the abdomen. Laboratory findings summarized in Table 37 show Plasma sugar 1452 mg per 100 cc, plasma acetone 4 plus, CO_2 combining power 12 volumes per cent, blood urea nitrogen 38 mg per 100 cc, glycosuria and acetonuria 4 plus, albuminuria 2 plus and many granular casts in the urine. The leukocyte count was 17650 per cu. mm of blood. There were 5080000 red cells per cu. mm, the hematocrit reading was 51 per cent and the specific gravity of the whole blood was 1.066.

Insulin. Insulin, with the exception of 200- and 100 unit doses administered early in the treatment, was given in doses of 50 units every half hour until the blood sugar was reduced to 377 mg per 100 cc. The totals amounted to 1350 units in the first twelve hours of therapy and 1750 units in the first twenty four hours. This amount of insulin far exceeds the quantity usually necessary to correct ketosis. It will be observed in Table 37 that there are no evidences that excessive amounts of insulin were given nor were there, at any time, clinical signs of overdosage. It was considered of utmost importance that large amounts of insulin be given frequently with ample carbohydrate as long as 4 plus reactions for plasma acetone were found. As the concentration of plasma acetone decreases the sensitivity to insulin increases, hence a lessening of the amounts of insulin as well as a reduced frequency of administration are imperative if hypoglycemic reactions are to be prevented.

Fluids. An extreme degree of dehydration was clinically manifest, the blood pressure was 90 mm Hg systolic and 50 mm diastolic and the specific gravity of the whole blood was 1.066 (normal 1.052 to 1.058). These studies when repeated indicated that despite the administration of unusually great amounts of fluids—2700 cc of normal saline in the first two hours of therapy and 6200 cc in the first six hours—the specific gravity of the whole blood was still elevated—1.059. Nevertheless with progress being otherwise favorable the rate of the administration of fluid was sharply reduced. The total volume of fluids—normal saline, plasma and glucose in distilled water—given in the first twelve hours reached a total of 8730 cc. In the second twelve hours of treatment fluids given by mouth amounted to 3900 cc., bringing the total in the first twenty four hours to 12630 cc. Less fluid in this latter period might have sufficed but with a urine volume of only 450 cc a smaller fluid intake was not justified. Also, dehydration was still manifest. The large output of urine in the first twelve hours was not attributable to excess fluid intake but rather to the diuretic influence of the hyperglycemia which prevailed. When this was alleviated the positive water balance was enhanced.

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5 00 P M	834		++++		41	1.059	++++	++++	1120
7 00 P M		33	++++		32		++++	++++	770
9 00 P M	37		++++		35		+	++++	150
11 30 P M	291		++++		35		0	++++	150
First 12 hours									3360
1 30 A M	28		+++		3		0	++++	150
3 30 A M	324		++		3		+	+++	—
5 30 A M	251	19	+				0	+	—
9 00 A M	186		+	26	36		+	+	300
Second 12 hours									450
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Total insulin administered: First 12 hours 1350 units

Second 12 hours 100 units

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Plasma During the first hour of therapy the blood pressure decreased to a systolic pressure of 80 mm Hg the pulse rate became very rapid and eventually the pulse was imperceptible. At this stage 350 cc of plasma was given. A gradual increase in the blood pressure to 110 systolic and 70 diastolic ensued.

Alkali Because of the intensity of the air hunger 600 cc of sodium racemic lactate solution was given intravenously. A dramatic improvement followed. The administration of alkali doubtless accounts to a considerable degree, for the elevation of the CO_2 combining power to 33 volumes per cent while the plasma acetone bodies, not so appreciably affected by this therapy, still gave 4 plus reactions. This illustrates one means by which alkali therapy may, on the surface, be misleading.

Glucose The intravenous administration of 5 per cent glucose solution—700 cc—was begun eight hours after therapy had been started. This was necessary, as the blood sugar had been reduced to 291 mg per 100 cc while 4 plus reactions for plasma acetone still prevailed. Subsequent carbohydrate intake was for the most part by the oral route.

Potassium Electrocardiographic tracings were made at the onset of therapy and frequently thereafter. Selected tracings of the second standard lead show a high T wave and a normal QT interval. In contrast with later electrocardiograms the high T wave was interpreted as indicating a hyperpotassemia—a common finding prior to insulin therapy and hydration in cases of diabetic coma. A tracing four hours later shows a reduction in the amplitude of the T wave. The QT interval remained unchanged. At seven hours the T wave was still further depressed, suggesting the early stages of hypopotassemia. Potassium chloride, 1 gm., was given orally at once and repeated every four hours for five doses. The amplitude of the T waves was normal four hours after the onset of potassium chloride therapy and remained so—the electrocardiogram being repeated at twelve and twenty four hours respectively. Prolongation of the QT interval in addition to progressive changes from reduced amplitude to flattening or even inversion of the T waves is a common indication of hypopotassemia (Fig 30). This change did not occur in this case. Possibly the early detection and correction of the hypopotassemia prevented the development of this characteristic.

In retrospect, and from the experience of others, formerly unexplained deaths in the second twelve hours of therapy in patients relieved of ketosis, and with no hypoglycemia, can surely be laid to hypopotassemia. These patients, despite their satisfactory blood sugar and CO_2 combining power levels, were unduly weak and apprehensive and, with a rather sudden onset of paralysis of the respiratory muscles, death followed quickly. Electrocardiographic tracings, taken frequently, afford an excellent means of detecting this dangerous complication hours before the clinical attack is likely to develop. Holler's³ patient developed paralysis of the respiratory

muscles and was in a respirator several hours when a very low serum potassium concentration was found. A dramatic recovery followed the administration of potassium chloride. Electrocardiograms present a much simpler method of detecting this abnormality than does quantitative analysis of the serum potassium. The work of Bellet and co-workers⁴ has made this clear.

The current explanation of the development of hyperpotassemia is the effect that during the intense dehydration potassium leaves the cells and with increased tissue protein breakdown hyperpotassemia and loss of potassium in the urine result. Hence, although the concentration of potassium in the serum is increased, the total body potassium is decreased.² But, when therapy is instituted the serum potassium is diluted, much is excreted with restoration of adequate hydration, cellular affinity for potassium is restored, and some potassium is used in the glycogen deposition in the liver and in association with protein deposition in the tissues. Hypopotassemia is likely to ensue.

Penicillin Because of the unexplained fever, and of the prophylactic value of penicillin, this drug was given during the acute phase of the illness.

Gastric Lavage This measure was not made use of as there was no history of vomiting or abdominal pain and there was no distention of the abdomen. An enema was given after consciousness was restored.

Progress Notes Improvements in the chemical values of the blood are noted in Table 37. Clinically, the recovery was slower than is usually observed. It was not until therapy had been carried out in an intensive manner for thirty-four hours that the patient was fully aware of her surroundings, though after fifteen hours she gave indications of understanding what was said to her. However, though in a semistupor she was able to take fluids by mouth after twelve hours of treatment and a liquid diet with values of 110 gm protein, 200 gm carbohydrate and 95 gm fat (2100 calories) was prescribed and given in four equal feedings—at six-hour intervals. The insulin also was administered at six-hour intervals. The diabetes was promptly controlled—fasting blood sugar value 66 mg per 100 cc.—with the diet outlined above and with 180 units of insulin daily.

There being no evidence of an acute complication remaining on March 11, the seventh day of therapy, a reducing diet—100 gm protein, 100 gm carbohydrate and 22 gm fat (1100 calories)—with supplementary minerals and vitamins was allowed. With this diet 110 units of insulin (60 units of protamine zinc and 50 units of regular insulin) daily maintained normal blood sugar values and freedom from glycosuria.

Pursuing our often repeated contention that an obese diabetic, and one who cannot attribute her obesity to insulin therapy, has a mild diabetes, and that obese patients are relatively insensitive to insulin, we did what one would not dare do in the case of a thin diabetic—we discontinued the 110 units of insulin abruptly on March 17 and gave none thereafter. Traces of

glycosuria occurred only on four occasions during the remainder of her hospital stay—eight days—and the fasting blood had increased only from 81 mg (March 17) to 113 mg (March 18). This patient was discharged on March 24 and when seen on the two succeeding weeks in the Out Patient Department she had reduced in weight an average of 1.9 kp. (4 lb.) per week. The blood sugar values were normal, the last being 117 mg per 100 cc., and there was no sugar in any of the fractional urine collections. Subsequent progress has been equally satisfactory (Aug. 1950).

Comment. This case illustrates the following:

1. That even though the diabetes is mild an acute infection, even as mild as an upper respiratory tract infection, may precipitate a dipterous ketosis.

2. That anorexia was an outstanding symptom of the ketosis and that it followed a period of excessive appetite.

3. That a \pm plus reaction for plasma acetone accompanying a \pm plus reaction for glycosuria in a comatose patient verified the clinical diagnosis of diabetic coma before it was possible to know the blood sugar value and the CO_2 combining power of the plasma.

4. That the rapidly deepening state of shock was ameliorated by the administration of blood plasma.

5. That renal decompensation—indicated by the elevated blood urea nitrogen, the albuminuria and casts—developed with progression of the peripheral vascular collapse.

6. That unusually large doses of insulin are tolerated during profound ketosis.

7. That many liters of fluid were indicated and that the administration was carried out rapidly while the need was great, using the specific gravity* of the whole blood—with correction for the degree of hyperglycemia—as a reliable indicator. While the values were above 1.075 rapid administration was permissible but would not be considered essential if the blood pressure was well sustained and the hematocrit value was nearly normal. More fluid, by far, was given to this patient than is usually the case.

8. That a conservative amount (600 cc.) of $\frac{1}{2}$ molar lactate solution promptly alleviated the intense degree of hypervolemia, and that despite this evidence of clinical improvement and an elevation of the CO_2 combining power to 43 volumes per cent, a \pm plus reaction for plasma acetone still maintained. This elevation of the CO_2 combining power is considered artificial and under these circumstances greater clinical value is placed on the qualitative—but crudely quantitative—reaction for plasma acetone. By testing serial dilutions of the plasma for acetone it is possible to secure a more accurate valuation of the amount of ketones retained in the blood.

9. That glucose therapy was withheld for eight hours because of the

* Determined by the falling disc method. A simple method of determining this value using varying concentrations of copper sulfate solution has been widely used.

severe degree of hyperglycemia. It is not considered that glucose given earlier would have been harmful but that it was unnecessary is obvious.

10 That hypopotassemia which is prone to develop as treatment progresses, is detectable with adequate clinical accuracy by electrocardiographic studies and that this dangerous abnormality is readily corrected by the oral administration of potassium chloride. It is quite probable that the degree of diuresis influences the risk of hypopotassemia. We suggest the routine use of potassium chloride given by mouth when renal excretion is good but withhold it in the event of oliguria or anuria unless there are electrocardiographic evidences of hypopotassemia. If the urgency demands potassium chloride may be given slowly intravenously—100 to 500 cc. of a 1.4 per cent solution—or subcutaneously.

11 That the uncomplicated obese diabetic can tolerate large amounts of insulin—in this case 110 units—which can be abruptly withdrawn with minor elevation of the blood sugar resulting while the patient is receiving a low calorie diet which, if continued brings the diabetes under perfect control.

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CHAPTER XVIII

Pregnancy Complicating Diabetes

Introduction. In the pre insulin eras pregnancy was infrequent in diabetic patients and if conception did occur gestation rarely proceeded to full term with a viable baby and without grave risks to the mother. But, with insulin therapy, and all that it permits, pregnancy is no longer uncommon. It carries little, if any, greater risk to the life of the diabetic mother than to non diabetic controls and the frequency with which full term viable babies are secured has increased greatly. But, stillbirths remain approximately six times as frequent with diabetic mothers as occurs with nondiabetics (White). It is to be noted, too, that although the mothers come through pregnancy without the former risk to life they are predisposed to eclampsia, hypertensive and renal disease, hydramnios and irritability of the uterus. Notwithstanding the progress that has been made, diabetes because of the degenerative changes associated with it and notably arterial and renal disease, and the tendency to hormonal imbalance, exerts far reaching effects on the course of pregnancy. Pregnancy, in these cases, is not a contract to be entered upon lightly, but barring the hazards of a diabetes of over twenty years' duration, premature arterial disease, hormonal disturbances which can to a large extent be neutralized, and the unpredictable congenital anomalies, the outcome is likely to be satisfactory. A satisfactory outcome depends considerably on the control of the diabetes, the adequacy of the diet, hormonal therapy when indicated, and the wise selection of the means of terminating the pregnancy.

The Diabetic Mother. Menstrual Irregularities. Delayed development of secondary sexual characteristics, amenorrhea, irregular menstruation, menorrhagia, and an early menopause are frequent in women with untreated or poorly controlled diabetes. However, with good control of the diabetes, catamenia is apt to occur at a normal age, or returns after a few months of amenorrhea, if the latter has been due to uncontrolled diabetes. In general, adequate control of the diabetes brings about a normal menstrual cycle in the great majority of these patients.

Fertility. Poorly controlled diabetes militates against conception but with better management of the diabetic patient fertility is improved. Despite this improvement diabetic women are somewhat less fertile than nondia-

betics Nutritional deficiencies associated with uncontrolled diabetes are probably a big factor in the production of sterility. Disturbances in hormonal relationships, especially a decrease in the amount of gonadotropic hormone of the anterior pituitary gland, are also considered to be important influences.

Abortion and Miscarriage Abortion and miscarriage are directly proportional to the lack of control of the diabetes. They occurred in 33 per cent of a series of uncontrolled diabetic patients, as compared with 2 per cent in patients whose diabetes was well controlled (White).

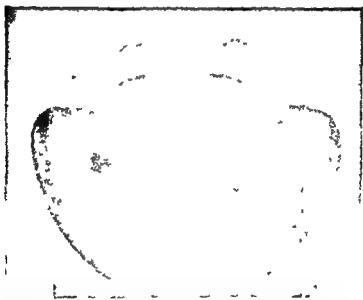


Fig 31 Calcified pelvic arteries in a diabetic woman fifty years of age.

Stillbirths and Toxemia Stillbirths are, despite insulin therapy, six times more common in diabetic than in nondiabetic women. Factors that operate to produce this are the tendency of the babies of diabetic women to be overweight, and also the remarkable frequency of hydramnios in these women. Diabetic patients are predisposed to toxemia by the prevalence of arteriosclerosis and of hypo-ovarianism which result in abnormalities of the sex hormones (excess serum chorionic gonadotropin). Calcification of the pelvic arteries (Fig 31), though not common, increases greatly the likelihood of stillbirths.

Abnormalities of Diabetic Pregnancies Vascular diseases and hypo-ovarianism are the most common abnormalities affecting the diabetic mothers. White¹ found evidences of vascular disease (coronary artery disease, calcified vessels, retinopathies and nephritis) in 70 per cent of her

patients whose diabetes began in childhood and was of twenty years' duration or more. Her rule for estimating the effect of the diabetes on the patient from an obstetrical point of view is as follows. Up to five years' duration of diabetes, the obstetrical diabetic patient can be considered the same as a nondiabetic as far as vascular disease goes. If the duration of the diabetes is five to fifteen years the amount of vascular disease to be expected makes the patient's physical age equal to the duration of the diabetes added to her actual age. If the diabetes is of fifteen or more years' duration, the chronological age is doubled to get the patient's physical age. Because of the serious vascular disease present in diabetic patients whose disease is of long standing, White² advises against pregnancy in a diabetic woman over thirty years of age, whose diabetes has been present twenty five years or more.

As a result of the hypo ovarianism which, like vascular disease, increases in severity with the duration of the diabetes, high levels of follicle stimulating hormone in the blood and low levels of 17 ketosteroid excretion in the urine are apt to develop. The result is that diabetic women tend to be gynecologically older than their stated age.

Chemical abnormalities of diabetic pregnancies are a low renal threshold for dextrose, and a disturbance of water balance. The low renal threshold which is physiologic in pregnancy and has been reported in 35 to 60 per cent of all pregnancies, can result in the excretion of large amounts of glucose in the urine while the blood sugar levels remain within normal range. When less than 100 grams of glucose are utilized daily, ketosis may result. The disturbance of water balance is shown by an excessive gain in weight followed by edema, hydramnios and fetal edema.

Mortality (a) **Maternal** In the pre insulin era, the maternal mortality was between 25 and 30 per cent, but now the maternal mortality, when the diabetes is properly controlled, is no higher than the 0.6 per cent which occurs in nondiabetic controls. *There is no excuse for diabetes in itself being responsible for a maternal death.*

(b) **Fetal** Abortions, miscarriages and stillbirths remain higher in diabetic than nondiabetic pregnancies. Furthermore, the fetal and neonatal mortality have been found to be as high during the five years preceding the onset of diabetes as after the disease developed.³ White⁴ has reported a fetal survival rate of 82 per cent in 433 consecutive diabetic pregnancies, but this varied with the occurrence of normal* or abnormal balance of sex hormones. If the sex hormones were normal the fetal survival was 95 per cent, if abnormal and uncorrected, the survival rate was only 58 per cent, if abnormal but corrected with estrogen and progesterone therapy, the survival rate rose to 89 per cent. In seventy eight fetal deaths (18 per cent) there were hormonal imbalances in 97 per cent of the mothers. 66 per cent of the mothers had onset of diabetes before they were ten years of age,

* Serum chorionic gonadotropin values not in excess of 200 rat units per 100 cc

52 per cent had had diabetes for more than ten years, 46 per cent had hypertension or albuminuria, 33 per cent had arteriosclerosis (20 per cent had arteriosclerotic changes in the pelvic vessels as detected by roentgen ray examination, Fig 29), 5 per cent had been in diabetic coma during the pregnancy and 1 per cent in eclampsia.

The Diagnosis of Diabetes Complicated by Pregnancy. When a pregnant woman develops diabetes, the diagnosis of this disease may be complicated because of the great frequency with which renal glycosuria occurs in normal pregnant women. The diagnosis of renal glycosuria as opposed to that of diabetes can be established by simultaneous determinations of the sugar in the blood and urine (see p 88). In questionable cases, glucose tolerance tests are indicated. A pregnant woman showing glycosuria, even with a normal glucose tolerance curve, but having a family history of diabetes, should be watched for the development of diabetes for several years.

The Effect of Pregnancy on the Diabetes. The effect of pregnancy on the diabetes is unpredictable. In some, the insulin requirement remains unchanged, in others it decreases, and in still others it increases.

In general, and if the diabetes is well controlled, we have found the need for insulin (a) to increase slightly during the first trimester—probably a reaction to endocrine readjustments, (b) to remain relatively stationary in the second trimester—the qualitative development phase for the child, and (c) to be increased in the third trimester—during the phase of quantitative growth with an overall increase in the total metabolism.

Occasionally the mother's diabetes appears to improve in the last trimester. It is probable that this is due to insulin provided by the fetus because, following delivery, the insulin need in these cases increases. Much more common is the steady increase in the insulin requirement during the last three months of pregnancy. This is an expected response to the increase in total metabolism accompanying the increase in the size of the baby.

Diabetes is not made worse by pregnancy if it is adequately controlled during the period of gestation.

Management of the Pregnant Diabetic Patient. General Measures. The regimen is, in general, the same for the pregnant diabetic woman as for the non pregnant. Good general hygiene and a reasonable amount of outdoor exercise are encouraged. The patient must be under close scrutiny by both the internist and the obstetrician throughout the pregnancy. She should be seen every two weeks during the first two trimesters, and every week during the last trimester.

Diet. In general, the diet should be adequate to prevent undernutrition during pregnancy and, as there is considerable evidence that diabetic patients need more vitamins than is usually the case, special care is taken to prevent vitamin deficiencies.

TOTAL CALORIES. These are calculated as for the nondiabetic (p 105)—

multiply the ideal body weight (see Appendix) in pounds by 10 and in case of pregnancy add 100 calories. The correction for activity will be varied according to the behavior of the body weight but for the initial diet 30 per cent of the basal diet is added. *Example* Patient twenty eight years of age, ideal weight 136 pounds

Multiply ideal weight by 10 (136×10)	1360
Correction for age and pregnancy add	100
	<hr/>
Basal calories	1460
Add 30 per cent for activity	438
	<hr/>
Total calories	1898

PROTEIN Multiply the ideal weight in pounds by $\frac{7}{8}$ to determine the protein in grams. In the illustrative case above this would be $\frac{7}{8} \times 136 = 119$ gm.

CARBOHYDRATE We prefer a liberal quota of carbohydrate, e.g., 250 grams or more. The calories not provided by protein and carbohydrate are supplied by fat, e.g.,

Protein 119×4	476 calories
Carbohydrate 250×4	1000 calories
	<hr/>
Calories from protein and carbohydrate	1476
Fat = $1898 - 1476 = 422$	$422 \div 9 = 47$ gm

DIETARY SUPPLEMENTS One quart of milk, or skim milk, is included in each day's diet to care for the need for calcium. Also, in view of evidences that diabetic patients may need more vitamins than nondiabetics, supplementary vitamins* are prescribed.

There is considerable latitude in the need for vitamins during pregnancy. The following amounts are regularly prescribed for daily use.

Vitamin A	6000 I U
Vitamin D	400 to 800 I U
Vitamin B Complex	Thiamine HCl 1.8 mg
	Riboflavin 2.5 mg
	Nicotinic acid 18 mg
Vitamin C	100 mg
Vitamin K	2 mg of synthetic vitamin K, intramuscularly at least four hours before delivery or preferably 2 mg daily for each of two days before delivery

Insulin We give insulin to every pregnant diabetic patient. The amount, brand and distribution are determined as for the non pregnant patient but special care is taken to keep the fasting and postprandial blood sugar values within normal ranges. This may require one to three injections of insulin daily.

In cases in which the insulin requirement increases steadily during the

* One therapeutic vitamin capsule (Squibb) on alternate days will provide adequate amounts of vitamins A, D, thiamine HCl, riboflavin, niacinamide and ascorbic acid. The supplemental administration of vitamins E and K has been recommended.

final trimester—the usual occurrence—a marked reduction in the need for insulin follows delivery. Contrariwise, when the severity of the diabetes appears to be greatly alleviated and the need for insulin decreases during the last three months of gestation delivery is followed by an increased severity of the diabetes and insulin must be given in increased amounts to control the diabetes and to avert ketosis (Duncan and Fetter) ⁵

The Management of Complications. Nausea and Vomiting. The nausea and vomiting of pregnancy has rarely been troublesome in our experience with these patients. Frequent feedings supplemented by glucose administered intravenously may be necessary to prevent ketosis. In this event a temporary schedule of four, or six, feedings in each twenty four hours with regular insulin before each is employed as in dealing with other acute complications (see p. 217). This program is usually not needed but when it is the normal or usual regimen is restored as promptly as is practicable.

Correction of Hormonal Imbalance. The relative merits of hormonal therapy, high protein diets with supplements and early delivery by cesarean section are not clear. Nevertheless, the combination of all three has afforded the best therapy to date for these patients and it is recommended for use until more effective measures are available and proven.

In White's ⁴ series of 439 cases, only 67 had a normal hormonal balance and therefore did not need substitution treatment. A severe diabetes of long standing favors the development of hormonal imbalance, which appears to be a faulty production of progesterone with poor production, or metabolism, of estrogens and compensatory high levels of serum chorionic gonadotropin—above 200 rat units per 100 cc. Unfortunately, the laboratory procedures necessary for the detection of a hormonal imbalance, viz., serum level of estrogen and chorionic gonadotropin, and urinary excretion of pregnandiol, are expensive and not available in most laboratories. Furthermore, the cost of the estrogen (diethylstilbestrol) and progesterone (proluton) in the doses recommended is often prohibitive.

Hormonal determinations—serum gonadotropin and quantitative excretion of estrogen and pregnandiol—should be made, if possible, in all pregnant diabetic women, and corrected if an imbalance is found. If the determinations cannot be made, we advise substitution therapy in all pregnant women with long-standing or severe diabetes, and in patients with a history of a previous obstetrical accident.

Estrogenic hormone is given to prevent the elevation of serum chorionic gonadotropin, and progesterone is given to prevent excessive destruction of estrogen.

The hormonal therapy recommended by White ⁴ entails the daily intramuscular injections of estrogen (diethylstilbestrol) and progesterone (proluton) according to the schedule outlined in Table 37.

ORAL ADMINISTRATION OF DIETHYLSTILBESTROL. A less expensive therapy has been recommended by Smith, ⁶ comprising the oral administration of

HORMONAL THERAPY ACCORDING TO CLINICAL CLASSIFICATION OF PREGNANT DIABETIC WOMEN*

I CLINICAL CLASSIFICATION					
	A	B	C	D	E
	1 Mild diabetes 2 No insulin 3 Little dietary regulation needed (5% of series)	1 Diabetes onset after 20 years of age and 2 Of less than 10 years' duration 3 Free of vascular disease (29% of series)	1 Diabetes for more than 10 years 2 Onset between 10 and 19 years of age or those with minimal vascular disease (44% of series)	1 Diabetes for 20 years or more 2 Onset under 10 years of age or considerable evidence of vascular disease (14% of series)	Calcified pelvic arteries (7% of series)
					All patients with nephritis (1% of series)
II SUBSTITUTION THERAPY					
Week of Pregnancy	Diethylstilbestrol and Proluton in Mg per day				
9-16	0	5		10	25
20-23	0	10		15	50
24-27	0	15		25	75
28-31	0	25		50	100
32 and up	0	50		75	125

diethylstilbestrol in doses of (a) 5 mg daily, by mouth, beginning during the sixth or seventh week of pregnancy (counting from the onset of the last menses), (b) the daily dose is increased by 5 mg at two week intervals to the fifteenth week (c) 25 mg daily in the fifteenth week (d) Thereafter the daily dose is increased by 5 mg at weekly intervals (e) Diethyl stilbestrol is discontinued at the end of the thirty fifth week

Treatment is begun not later than the sixteenth to the nineteenth week and the initial dosage is always the one for the particular week of pregnancy according to the plan of therapy outlined above

Salt Restriction A moderate restriction of the daily salt intake, not more than a total of 3 gm if edema is present and even greater restrictions are exercised if the retention of salt and water assumes more than a mild degree. In addition, courses of ammonium chloride—4 to 8 gm daily for three days—are given as needed with rest periods of two or three days between courses

Termination of Pregnancy The choice between permitting spontaneous delivery and delivery by cesarean section is not always an easy one. Barring obstetrical contraindications we prefer spontaneous deliveries when

- (a) the mother has had a previous and successful confinement, and
- (b) when the diabetes is of recent onset and there is a normal concentration of chorionic gonadotropin in the serum and with no signs of toxemia

Following White's lead, cesarean section early in the thirty eighth week is recommended for

- (a) primiparae
- (b) pre eclamptic patients with increasing blood pressure, edema and albuminuria
- (c) those in whom the chorionic gonadotropin has not been reduced to normal
- (d) those who have had previous abortions or stillbirths and no successful full term pregnancies, and
- (e) if the baby appears to be unusually large

The risk attending a cesarean section is extremely small. Furthermore, the management of the diabetes is subjected to less disturbance by this method of terminating the pregnancy than if normal labor is permitted.

These rules almost identical to those advocated by White, simplify the problems surrounding the termination of pregnancy and have led to gratifying results.

Treatment During Labor and Delivery The patient is given the equivalent of 10 to 15 gm of carbohydrate per hour during labor, which amounts to 150 to 200 gm if the labor is long. The carbohydrate is given by mouth if practical. Otherwise it is administered intravenously as 10 per cent dextrose in normal saline solution or distilled water. Regular insulin is

given in small doses at four hour intervals, the amount being increased or decreased according to whether sugar is present or absent in each specimen of urine. Exact control of the diabetes is not important for the short period involved. The aim is to prevent (a) ketosis and (b) hypoglycemia.

Anesthesia Ordinarily, caudal anesthesia is employed for spontaneous vaginal deliveries and spinal anesthesia for delivery by cesarean section.

Treatment During the Early Postpartum Period A prompt reduction in the insulin requirement occurs in most patients after delivery, and especially in those whose insulin requirement increased in the final trimester of pregnancy. Obese patients who required large amounts of insulin during pregnancy can usually get along without it within a few days after delivery.

Lactation Diabetic women lactate poorly even though the diet is ample. Supplementary feedings are needed if the mother nurses her baby, a procedure which is not advocated for diabetic mothers. The deficiency of milk may be due to a decrease in the lactogenic hormone of the anterior pituitary gland. The diabetic mother who nurses her baby needs less insulin than she did before she became pregnant. Since lactose in the urine may be mistaken for glucose, and since the lochia renders the urine unsuitable for examination during the early postpartum period, frequent blood sugar determinations are needed to guide the insulin dosage in the lactating mother.

Postpartum Complications Eclampsia may develop in the postpartum period. It is treated, if it occurs, as in the nondiabetic, with intravenous injections of dextrose solution and of concentrated human albumen (salt free), oxygen therapy, intramuscular injections of 50 per cent magnesium sulfate solution and sedatives. Pyelitis and pyelonephritis are the most common causes of postpartum fever in the diabetic patient. Sulfonamides or streptomycin are indicated as in the nondiabetic (see p. 193). Puerperal fever, a rare combination, is also treated as in the nondiabetic. While infection persists the insulin dosage is increased as need be and the patient should be placed on the regimen for patients with acute complications (see p. 214).

Care of the Newborn Infant of the Diabetic Mother The infant born to a diabetic mother needs special care. The chief dangers of the neonatal period are hypoglycemia and asphyxia. Compensatory overactivity of the fetal pancreas with resultant hypoglycemia in the infant is doubtless the result of inadequate control of the mother's diabetes during the last trimester of pregnancy. Exact control of the mother's diabetes during gestation tends to prevent hypoglycemic attacks in the newborn infant. It is wise to give the infant feedings of a 5 per cent aqueous solution of lactose, through a medicine dropper, every two hours from birth through the first three days of life. The use of lactose water obviates the need for intramuscular or subcutaneous injections of dextrose solution.

Respiratory difficulties, with a tendency to asphyxia, occur more often

in infants born of diabetic than of normal mothers. Ketosis, hypoglycemia, or trauma to the cerebral cortex from a long labor associated with a large baby may contribute to the production of asphyxia. In White's series, 60 per cent of the infants showed some degree of respiratory difficulty. Special care in removing mucus from the infant's mouth and throat by suction and postural drainage, and the use of an incubator, in which the temperature is 29° C (84.2° F) and the atmosphere contains a large amount of oxygen, will reduce the danger of asphyxia.

Fetal Anomalies Congenital defects are unduly frequent in babies born of diabetic mothers. White reported that twenty two of 123 babies born to diabetic women had twenty six congenital defects. Thus one - defect, compared to one in fifty.

born to diabetic mothers are often unusually large in late pregnancies. White found that 80 per cent of the infants exceeded the normal weight. The length of these babies as well as the weight, exceeded normal. The overweight was considered to be due to fat edema and splanchnomegaly, the latter being most marked in the liver, spleen and heart. Microscopic evidence of hematopoiesis of the spleen and liver was seen in fourteen of the seventeen infants upon whom autopsies were performed. Atelectasis was observed in thirteen, persistence of fetal glomeruli in six, and hyperplasia of the islets of Langerhans in five. These infants showed the general appearance of postmaturity: long hair, double eyelashes, atelectasis, and enlargement of the spleen. Miller and Wilson have likewise reported cardiac hypertrophy, excessive erythropoiesis in the liver, and hyperplasia of the islets of Langerhans in babies born to diabetic mothers. These findings were most frequent in the large babies.

Outlook for the Child If the infant of the diabetic mother is born alive, its chances of survival are nearly as good as those of infants born of normal mothers, and the mortality during the first year of life of babies born of diabetic mothers is the same—5 per cent—as that for babies born of nondiabetic mothers (White).

Diabetes is transmitted as a recessive Mendelian trait. Hence the child cannot inherit the disease from the mother alone. Unless the father has diabetes also, or carries a recessive factor for diabetes, the child will not develop the disease.

Summary. Although good control of the diabetes in the pregnant woman has reduced the maternal mortality to almost nil the incidence of abortions, miscarriages and stillbirths remains much higher than in non diabetic women. This high fetal mortality is due to the high incidence of toxemia in diabetic women, which in turn results from the high incidence

* Extent of the newborn infants of diabetic mothers in need of medical help is a common occurrence. It has not been a common complication in our cases.

of vascular disease and the frequent imbalance of sex hormones. The latter can be successfully treated with estrogenic hormone and progesterone, but so far the problem of vascular disease in long standing diabetes has not been solved. During pregnancy, there is an increase in the insulin requirement, especially in the first and third trimesters, and after delivery the insulin requirement usually decreases rapidly. With adequate control of the maternal diabetes during the last trimester, overactivity of the islets of Langerhans of the fetal pancreas is probably prevented, and the risk of hypoglycemia in the newborn baby thereby decreased. We favor normal spontaneous delivery in diabetic women, unless an indication for cesarean section aside from the diabetes exists. The newborn infant of the diabetic mother needs special care to prevent the development of hypoglycemia and asphyxia.

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CHAPTER XIX

The Diabetic Child

INTRODUCTION—INCIDENCE—SPECIAL RISKS

The child with diabetes poses problems which are often more complicated than those presented by the adult diabetic. Relatively, the child is in a state of metabolic and psychologic instability. He is subject to changes that accompany growth, to fluctuations in metabolic and emotional patterns, and to the inability of the immature mind to comprehend the problems which diabetes presents.

Diabetes is uncommon in children. One child in two thousand under the age of fifteen, regardless of sex, may be expected to develop diabetes. The incidence is slightly higher in the Jewish segment of the population.

A prompt diagnosis followed by adequate treatment eliminates mortality due to diabetes in children. However undiagnosed and passing as "nephritis," "bed wetting" or a "behavior problem," diabetes in children may be complicated by a ketosis with great rapidity. But, even at this stage if the dialadies—diabetes and ketosis—are identified, prompt therapy, though more complicated, is successful in restoring good health.

ETIOLOGY

The influence of heredity in the development of diabetes is established. An heredity factor is the outstanding and possibly the only common predisposition to diabetes in childhood. Unlike in the adult, obesity plays no apparent part in precipitating diabetes. A clear cut history of diabetes in the family is not always obtained. There are obvious reasons why this should be, but one important one is that the parent, or parents, may not develop clinical diabetes until long after the child has been under treatment for this disease. Entire families having diabetes, the almost simultaneous development of diabetes in twins and family trees spotted with diabetes are inescapable evidences of the influence which heredity exerts. Furthermore, the studies of Pincus and White¹ have shown that the development of diabetes follows a Mendelian pattern and with recessive characteristics.

Overactivity of endocrine glands has a less secure place as an etiologic factor in precipitating diabetes. However, children are taller than normal

at the onset of the disease. Also, these children exhibit bone development in advance of their ages and secondary sexual characteristics develop prematurely, and ketosteroid excretion values tend to be higher than in non-diabetic children of the same age. To blame the pituitary gland is inviting and it is highly probable that this gland plays a part, even if not the predisposing part, in producing clinical diabetes.

There is no evidence that infection causes diabetes.

SYMPTOMS

The symptoms of diabetes in children are more sudden in onset and more marked in their severity than in the adult. Cases with an insidious onset do occur but they are uncommon. We have seen one such patient who had been treated for "nephritis" for four months because of nocturia.

In the infant, who cannot make his complaints known, the possibility of diabetes should be kept in mind when thirst and weight loss are marked. Older children may complain of being tired, an inability to "keep up," aching in the extremities, and headache. Excessive thirst, hunger, frequency of urination and loss of weight are the most consistent group of symptoms. Loss of weight, in child or adult, in the presence of an increased ingestion of food, is suggestive of diabetes mellitus, although the other causes of loss of weight, notably intestinal and nutritional disorders and overactivity, are not to be disregarded. Occasionally, the diabetic child is in coma due to ketosis when first seen by a physician. This is particularly true when some other complication, notably an acute infection, may attract the parents' attention and at the same time intensify the speed with which ketosis develops. In such cases diabetes may even escape the physician's attention if he does not make a routine practice of examining the urine. In these cases the excessive appetite gives way to anorexia, nausea, and often vomiting. Extreme degrees of lassitude and somnolence. The frequent passing of large quantities of urine is an invariable symptom and continues well into the ketotic phase and until the dehydration is of such a degree that it tends to reduce the amount of urine produced.

DIAGNOSIS

The acuteness of diabetes in childhood increases the likelihood of a prompt examination, the polyuria attracts attention to the urinary tract, and glycosuria is found. The renal threshold for sugar is not elevated in children and if the urine is examined during the course of symptoms sugar will almost invariably be found. Specimens voided two to three hours

Glycosuria having been found, the diagnosis is confirmed if concentration of sugar in a sample of venous blood taken before breakfast exceeds 130 mg per 100 cc, or if in excess of 160 mg per 100 cc if the blood is

taken after a normal meal. If there is doubt about the diagnosis, a test meal (see p. 79) may be given, and if the diagnosis is still not clear a glucose tolerance test (see p. 82) is done, giving 1.75 gm. of glucose per kilogram of the normal body weight. The spacing of the blood sugar determinations and the interpretation of the test are the same as for the adult (see p. 82).

PREVENTION

There is no known practicable means of preventing diabetes in children. To be successful in preventing diabetes, diabetics and persons predisposed to diabetes by heredity would need to marry into nondiabetic families. This impracticable plan, if continued for several generations, would tend to delete diabetes. There is no convincing evidence that diet restrictions or additions play any part in preventing diabetes in children.

TREATMENT

The successful treatment of the juvenile diabetic entails a special understanding of the disease process in the child and an appreciation of his attitude towards the disease, towards treatment, towards his playmates and towards life.

The success of therapy will depend largely on the ability of the physician to secure the confidence of the child. Special needs for the growing and developing child—the physical and mental needs—are to be considered. Furthermore, the regimen should be as flexible as is practicable and should be shaped in such a way that a reasonably normal life and normal childhood activities are possible. The criteria of good control for a diabetic child are:

1. Adequate nourishment.
2. A fasting blood sugar level below 150 mg. per 100 cc. and post prandial levels below 200 mg. per 100 cc.
3. Freedom from "major" or consistent glycosuria.
4. Cholesterol content of the blood below 230 mg. per 100 cc.
5. Normal physiologic and psychologic adjustment and development.

Our practice has been to admit all new diabetic children to the hospital for a period of standardization and training. Under ordinary circumstances this is the wisest procedure. However, if adequate facilities for metabolic studies and instructions in diet and insulin therapies are available in the outpatient service or physician's office, there may be certain advantages to providing the instruction with the patient carrying on his normal activities. The child learns to live with his disease in his home environment and the problems of management can be solved as they arise. This prevents the necessity for a second period of adjustment after discharge from the hospital. During this period frequent visits to the office are necessary—as often as three or more visits per week—for the first few weeks. This is

at the onset of the disease. Also, these children exhibit bone development in advance of their ages and secondary sexual characteristics develop prematurely, and ketosteroid excretion values tend to be higher than in non diabetic children of the same age. To blame the pituitary gland is inviting and it is highly probable that this gland plays a part, even if not the pre disposing part, in producing clinical diabetes.

There is no evidence that infection causes diabetes.

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essential not only in the solution of problems as they arise but also because there is a marked tendency for a reduction in the insulin requirement to occur during the first two weeks of adequate management. Close checks on the blood sugar levels and glycosuria at frequent intervals are advisable in order to anticipate and prevent hypoglycemic reactions.

Diet. Unlike the adult the child is constantly adding to the size of his body. Adequate dietary provisions are taken into consideration for this continuing and variable growth. Special attention is given to the protein content of the diet and to the total calories as requisites for normal development. Carbohydrate is scarcely less important as a source of energy. Fat is chiefly important as a source of calories.

TABLE 39
ENERGY REQUIREMENTS OF CHILDREN*

Total Calories for Children According to Body Weight				
AGE IN YEARS	CALORIES PER KILOGRAM		CALORIES PER POUND	
1-2	100-90		50 13	
3-5	90-80		40 36	
6-9	80-70		36 32	
10-13	70-60		32 27	
	Boys	Girls	Boys	Girls
14-15	60-55	50-45	27 23	23 20
16-17	60-55	45-40	27-23	20-18
18-19	55-50	40-35	25 23	18 16

* Rose. *Foundation of Nutrition*. The Macmillan Company, 1933.

Calories. The child, because of his great expenditure of energy, his needs for growth and his relative increased surface area per unit of body weight, needs more calories per kilogram than those who are fully grown. The very high requirements of infancy and early childhood fall gradually until after puberty, they reach the adult levels. These considerations are indicated in Table 39.

Protein. Protein is "construction material"—an essential for growth. Modern dietetic practice is tending toward more generous allowances of protein for adults as well as for children and there are reasons to believe that this will lead to better development, better health and increased longevity.

The daily protein allowances for children are from a minimum of 20 gm per kilogram of the normal weight to 30 gm per kilogram (0.9 to 1.1 gm per pound). Larger quantities of protein are permissible during the correction of malnutrition and patients with a "labile diabetes" are less likely to have hypoglycemic reactions if the protein content of their diets

is high. Presumably this benefit derives from the slow delivery of carbohydrate from protein foods.

Carbohydrate. All diabetic children need insulin. Hence there need be no severe restriction of the carbohydrate quota when, for a few more units of insulin, nearly normal amounts of carbohydrate are well tolerated.

The maximum daily carbohydrate allowance is 320 gm. Until this maximum is reached we prescribe 50 per cent of the total calories as carbohydrate.

The distribution of the carbohydrate in the diet for the child is the same as for the adult (see p. 103). It is always permissible to save part of any meal for consumption two or three hours later. Regularity of the quantitative distribution of carbohydrate from day to day is an important feature in preventing needless risks of hypoglycemia, or of extreme degrees of hyperglycemia.

Ordinarily diabetic patients are advised not to eat sugar, the reasons being that it is a very concentrated food, devoid of vitamins and minerals, and takes the place of bulkier foods containing both of these accessory food factors. However, we have no objection to the use of cane sugar in small and appropriate amounts when it is desirable to reduce the bulk of the diet and provided precautions are taken against the development of mineral and vitamin deficiencies.

Fat. Fats are important as sources of calories, fat soluble vitamins, essential fatty acids, and as a great addition to the palatability of the diet. The diabetic child has a tendency to hypercholesterolemia and an excess of fat in the diet may accentuate this trend. Approximately 20 per cent of the total caloric content of the diet is in the form of fat and the main sources are dairy products, margarine and meat. If the hypercholesterolemia is marked and persistent, even after the institution of insulin therapy, the amount of fat is reduced in favor of a more liberal carbohydrate quota and the fatty portions of meats, which are high in cholesterol, are eliminated.

Minerals. The demands for minerals are high in the growing child. Infants need 6 mg. of iron per day and the need increases to 20 mg. daily during periods of maximum rate of increase in weight. Adequate amounts of calcium and phosphorus will be supplied by one quart of whole milk daily in addition to the other dietary constituents.

Vitamins. If the protein, fat and carbohydrate needs of the child are met from natural foods, well prepared, and containing liberal amounts of milk and raw fruit and vegetables, there need be no concern about the possibility of vitamin deficiencies. However, methods of preparation, seasonal variations in the quality of foods, and the availability of simple complete vitamin supplements have led us to employ routinely a multiple vitamin supplement capsule daily in the treatment of children with diabetes.

Insulin. All diabetic children need insulin therapy. Practically all dia

betic children succumbed within two years to the disease in the pre insulin eras. In general the principles governing insulin therapy are the same for the child as for the adult. The criteria for good control and the speed and duration of insulin action are the same. However, there are relatively stable homeostatic mechanisms which tend to provide a wide margin of safety between a hypoglycemia and a hyperglycemia in most adult diabetics which are not nearly so efficient in the child. As a result the concentration of sugar in the blood of a child diabetic is much more labile and may change rapidly from a high level to a low one or vice versa. Furthermore these changes are set in motion by conditions which in the adult would have little effect, e.g., a change of 2 or 4 units of insulin, physical exercise and delayed meals. In fact, all influences which tend to change the insulin requirement (see p 43) tend to have a more intensive effect on the child than on the adult.

Some adult patients have diabetes that has the labile* characteristics of diabetes in the child.

The small margin of safety between hypo and hyperglycemia in the child is doubtless related to the smaller supply of glycogen on one hand and to the amount of physical exercise indulged in on the other. It is because of this narrow margin of safety that mild degrees of glycosuria are considered advisable as indications of security against hypoglycemic reactions. The amount of glycosuria need not exceed 10 gm daily if there is appropriate timing of the meals and insulin as illustrated on pages 108 to 111.

The selection of the insulin regimen is much the same as that for the adult. In practically no case does a single dose of protamine zinc insulin control the diabetes satisfactorily. A single dose of globin insulin is satisfactory in a small number of cases. A mixture of protamine zinc insulin and regular insulin 2:1 or occasionally 3:1, is more effective than a single dose of either protamine zinc insulin or globin insulin. One relatively large dose of globin insulin one hour before breakfast and a very small dose before supper is satisfactory in some cases. A mixture of protamine zinc insulin and regular insulin 2:1 (or 3:1) fifteen minutes before breakfast and a small dose of regular insulin before supper is a most effective plan of therapy.

However, very good results have been secured with a mixture of NPH

diabetic

patient (see p 108)

Checking the control of the diabetes is effectively done by securing on the test day—usually within a day or two before discharge from the hos

* These cases of labile diabetes are often referred to as brittle diabetes—a poor term.

pital—a blood sugar value before breakfast and one at 3 P.M., and by testing a specimen of urine voided before each meal and at bedtime for sugar.

The fasting blood sugar value is an index of the adequacy of the previous day's dose of protamine zinc insulin, the 3 P.M. value will indicate the effectiveness of the morning dose of globin insulin. The presence or absence of glycosuria just before lunch is a check on the morning dose of regular insulin, the results of testing the urine voided before supper and at bedtime are further checks on the effect of the morning dose of globin or NPH insulin.

Determination of the sugar values of blood withdrawn before each meal and at bedtime provides a more critical check which is used occasionally.

The results of the foregoing tests not only indicate the degree of control of the diabetes but may indicate a change of the type of insulin or a different distribution or a mixture may be suggested.

The needs of the child diabetic are more subject to change than those of the adult. Each office visit should be the occasion for checking the blood sugar, fractional urinalyses, body weight, rate of growth (Fig. 32), physical activities and general health.

Home reports are kept by the patient when practicable, or by a parent when necessary. One testing of the urine daily is desirable and a test before each meal and at bedtime is done one day per week. The latter method is adopted daily in the event of any complicating illness or if the tests reveal large amounts of glycosuria. The results serve as an index upon which to base a change of insulin or diet, or both.

Exercise. The importance of normal exercise in the physical, mental and social development of a child is great and the diabetic child should not be excluded from these activities. The modern treatment for diabetes makes it possible for the child to fit into group or individual athletics in a normal manner. One of our patients was a star performer on his high school swimming team, another is an enthusiastic tackle on the 80-pound squad. A nationally famous tennis player has a severe grade of diabetes.

Physical exertion reduces the blood sugar in addition to, and independent of, the insulin activity in operation at the time. Violent physical exertion is therefore likely to produce a hypoglycemia unless an adequate adjustment in diet or insulin, or both, is made in advance. Since there is no appreciable harm to be expected from a transitory hyperglycemia it is our practice to supply an excess of readily available glucose by mouth just before the exercise is begun. An apple or a banana is not only permissible but desirable. A candy bar is even permissible before a strenuous game or a long hike. A short period of hyperglycemia is to be preferred to the risk of an insulin reaction. This precautionary measure is particularly important prior to swimming where the exercise may be prolonged and where the apparent danger from a hypoglycemia is increased.

Education. These children are usually intellectual beyond their years

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However, very good results have been secured with a mixture of NPH insulin and regular insulin, 4 1, given approximately fifteen minutes before breakfast—the mixture being made at the time of administration.

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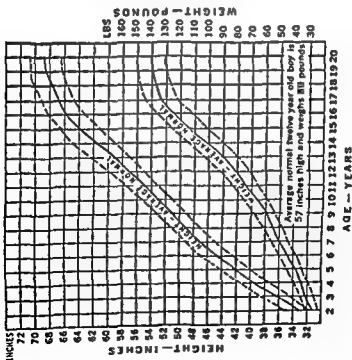
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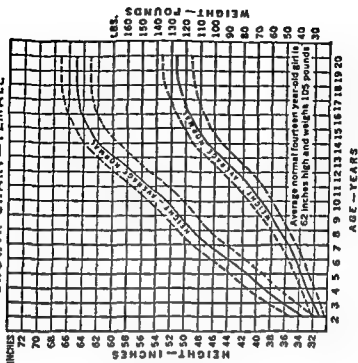
Education. These children are usually intellectual beyond their years.

GROWTH CHART—MALE



Solid lines indicate average normals, broken lines, 100 percent above or below ideal normals

GROWTH CHART—FEMALE



Solid lines indicate average normals, broken lines, 100 percent above or below ideal normals

Fig 22 Normal growth patterns. (Presented through the courtesy of Dr J H Barach.)

and frequently their understanding is better than that of adults. Their limitations should be stressed only enough to lead them to take sensible precautions. Thus the circumstances under which hypoglycemia may develop (exercise or delayed meals) should be explained and adequate preventive measures described. The reason for insulin and the dangers of omitting a dose are pointed out. By the age of eight or ten years the child should be giving himself the insulin injection and should be capable of performing the urinalyses required. The Clinistest method of testing for sugar is simple and can be performed at an early age. Familiarity with the food exchanges and a knowledge of the flexibility they permit give the young as well as the older patient great reassurance.

As the child matures it is well to guide him, if possible, into an occupation not requiring contact with power-driven machinery or irregular hours of dining or sleeping. The use of tobacco should be discouraged since there are many reasons to believe that this habit may accentuate the vascular troubles that so frequently develop in adult life.

Reassurance, commenting on favorable progress at school and in sports are valuable in developing and increasing a will to follow the pattern of living which will not be completely normal but will afford, to these young patients, opportunities to excel which would otherwise be denied.

Special Considerations. With control of the diabetes there tends to be a decline in the insulin requirement during the first few weeks. Thereafter, as the child grows, the general tendency is for the insulin requirement to increase, more or less in proportion to the increase in size of the body.

In some girls there may be a tendency to hypoglycemia just before the menstrual period. In others the opposite is true. Usually these tendencies will be quantitatively consistent from month to month so that provisions can be made by altering the dose of insulin at the appropriate time.

As the child grows his requirements for food as well as for insulin, gradually change and the diet should be reviewed at intervals of not longer than six months, in the light of changes in weight and age. As adolescence is passed the diet should be based on adult requirements.

All of these children should wear engraved metal identification bracelets. A suitable inscription might be:

Front: I take insulin. If I am sick or faint give me sugar. Call a doctor (over).

Back: Name and address.

The education, training and adjustment of the diabetic child can be expedited by a summer or two at a camp for diabetic children. Many of these camps, with a leguate medical and educational personnel, are coming into existence. Here the child by being with other diabetic individuals, loses his sense of being handicapped. He is taught that he can live with, and make light of his extra load. The stimulus to becoming self-sufficient is great under these conditions and a fretful, resentful child frequently be-

comes proud of his ability to cope with his disease. Every child with diabetes, who is otherwise healthy, should be given an opportunity to attend a diabetic camp.

COMPLICATIONS

Ketosis. Children suffering from diabetes are, generally speaking, more prone to develop ketosis than are adults. This is because of (1) the 'labile' character of their disease, (2) the greater variety of circumstances which will upset their regimen, (3) the greater frequency of intercurrent febrile diseases, and (4) fluctuating severity of the diabetes itself.

The more common precipitating causes of diabetic coma are

(a) Infections causing loss of appetite—added to this, the insulin may be erroneously omitted. A dose of insulin is never to be omitted while glycosuria is present. If a patient cannot take food, one half of his usual dose of insulin is taken and a small amount is taken every four hours until seen by a physician, if strong reactions for glycosuria prevail. The management of the diabetes during acute complications is the same for the child as for the adult (see p. 212).

(b) Errors in the dosage or the complete omission of insulin.

A word of caution is sounded regarding abdominal pain in the juvenile diabetic. This symptom is frequently encountered in cases of ketosis in child diabetes. Abdominal pain, vomiting, splinting of the abdominal muscles and leukocytosis mimicking an acute appendicitis in detail are promptly corrected if due to ketosis by relieving a distended stomach and by administering sodium chloride. If relief is not prompt the possibility of an acute surgical condition is greatly enhanced.

Surgical Complications. The management of the diabetes during surgical complications is the same for the child as for the adult (see p. 221).

Miscellaneous Considerations

1 Diabetic or Pseudodwarfism. Uncontrolled and severe diabetes in early childhood causes a stunting of physical growth—a pseudodwarfism. Growth, sexual and osseous development are retarded. The abdomen is protuberant and there is enlargement of the liver. Obesity frequently develops after the diabetes is controlled.

The cause of this pseudodwarfism is not known. Malnutrition, secondary to the diabetes is doubtless an important factor. Hypogonadism is indicated by the reduced excretion of ketosteroids but there are evidences of activity of the anterior pituitary gland and the basal metabolic rate tends to be elevated. Nevertheless a decrease in the growth hormone is a probability.

Treatment. Control of the diabetes and more liberal quotas of protein than are usually prescribed are advisable. Supplementary vitamins are given and thyroid therapy is tried very cautiously. It is doubtful if the benefit observed is actually due to the thyroid medication.

White reports good results from the intramuscular injections of pituitary extracts so long as the epiphyses are open but that after seventeen years of age puberty is precipitated with therapy but physical dwarfism remains. Testosterone propionate* causes accelerated growth in retarded boys.

2 Hepatomegaly. Enlargement of the liver is uncommon when the diabetes has been well controlled. The liver may be quite large, extending into the pelvis, and its edge is firm, sharp and slightly tender. The enlargement is due to excessive deposits of glycogen, or fat, or to hydropic degeneration. The function of the liver is not grossly impaired. The liver usually reverts to normal size following a short period of good control of the diabetes, but this transition is accelerated by administering lipotropic substances. Our experience is chiefly with choline in doses of 2 gm. three times daily.

3 Premature Degenerative Changes. The incidence of degenerative disease in adults who have had diabetes since childhood is extraordinarily high. Premature arteriosclerosis is the most common of these changes, though the incidences of retinitis and of renal disease are also higher than in those who acquired diabetes after childhood.

Juvenile cataracts, though rare, develop with great speed and always in those children with poorly controlled diabetes. The opacity involves the anterior and posterior portions of the optic lens and leads to great impairment in vision. The treatment depends on the stage of development of the disorder when detected. Control of the diabetes may halt its progress, "needling" of the lens may be effective, or surgical removal may be necessary.

So far, the only preventive measures that offer optimistic results against the foregoing degenerative disorders are (a) control of the diabetes and (b) the correction and prevention of hypercholesterolemia. These aims are achieved by having these young patients take diets high in carbohydrate—300 to 400 gm.—high in protein and low in fat—not in excess of 50 gm.—with appropriate insulin therapy.

PROGRESS OF THE JUVENILE DIABETIC—FACTS AND PRINCIPLES

The juvenile diabetic is brought face to face with responsibilities of the adult. Despite the best of intentions and efforts of all concerned a barrier or modifying influence conditions his activities somewhat and as a result the occasional child becomes introspective, moody and emotionally unstable. A sympathetic understanding with good disciplinary training on the part of the wise parent dissipates the child's frustration and makes him the key person on the team—the patient, parents and physician. With adolescence and maturity his better than average intelligence works in his favor—situations are easier to handle, his ego is less sensitive and he develops self-confidence. Instead of feeling restricted and hemmed in by the differences which exist between him and other children he begins, with or before adolescence, to accept responsibilities. The acceptance of responsi-

* Oreton (Ciba), 25 mg. two or three times weekly for two or three years.

bility when the adolescent gets his first position and earns his first money, or when he or she falls in love or experiences some other maturing influence, has a favorable influence on the control of the diabetes

Finally, a normal approach to marriage and parenthood is encouraged with an understanding of the part played by heredity in causing diabetes and of the special care necessary during pregnancy if it is to come to a successful conclusion

TABLE 40
DIABETES IN CHILDREN CONTRASTED WITH DIABETES OCCURRING IN ADULTS

	CHILDREN	ADULTS
Onset	Abrupt	Usually gradual
Weight	Normal	Approximately 70 per cent are overweight
Stability	Diabetes labile	Diabetes usually relatively stable
Insulin	Necessary for all	Approximately 15 must take inulin
Coma	Relatively frequent	Infrequent
Sensitivity to Minor Changes	Very sensitive	Relatively insensitive
Family History of Diabetes	Very common	Common
Degenerative Changes	Infrequent	Common
Hepatomegaly	Common	Relatively uncommon
Control of Diabetes	Difficult	Easy
Control of Food Intake	Difficult	Relatively easy
Variations of Activity	Great	Small

OUTLOOK FOR THE JUVENILE DIABETIC

The outlook for the juvenile diabetic is excellent in contrast with that of the pre insulin era. Diabetic children, wisely treated, grow in a normal manner. They do better than the average student in school. Professional or other independent careers are encouraged, thereby circumventing or reducing the possibilities of being refused employment because of the diabetes. Ordinarily, diabetic individuals do well at any occupation but it is unwise for them to be exposed to power driven machinery and equally unwise to select a position or profession which by its nature entails irregular living, meals, physical activities and traveling, e.g., a diabetic who becomes a physician should not practice obstetrics or do general practice but institutional work, permitting regularity of meals and hours, would be quite satisfactory.

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- 2 White P. *In Treatment of Diabetes Mellitus* by E P Joslin and associates. Lea & Febiger Co., Philadelphia 1916 p 760

Appendix

HEIGHTS AND WEIGHTS OF CHILDREN BETWEEN ONE AND FOUR YEARS OF AGE (WITHOUT CLOTHING)

5602 Boys		Age Months	4821 Girls	
Height, Inches	Weight, Pounds		Height, Inches	Weight, Pounds
26.5	18.0	6	25.9	16.8
27.3	19.1	7	26.5	17.4
27.6	19.8	8	27.0	18.3
28.1	20.4	9	27.6	19.1
28.5	20.9	10	27.9	19.5
29.0	21.4	11	28.4	20.1
29.4	21.9	12	29.0	21.8
29.9	22.9	13	29.4	21.0
30.5	23.0	14	29.5	21.6
30.8	23.6	15	30.1	21.9
31.1	24.1	16	30.5	22.0
31.4	24.5	17	30.8	22.9
31.8	25.6	18	31.1	23.4
32.3	25.5	19	31.5	23.8
32.6	25.8	20	32.0	24.1
32.9	25.8	21	32.3	24.8
33.3	26.9	22	32.6	25.3
33.6	27.0	23	32.9	25.6
33.8	27.1	24	33.4	26.4
34.0	27.9	25	33.8	26.9
34.1	28.3	26	33.9	27.3
34.8	29.0	27	33.9	27.3
35.1	29.1	28	34.4	27.8
35.4	29.3	29	34.8	27.8
35.4	29.5	30	34.9	28.3
35.5	30.3	31	35.1	28.8
36.0	30.6	32	35.4	29.0
36.1	30.6	33	35.6	29.1
36.5	31.1	34	36.5	30.1
36.8	31.9	35	36.5	30.3
37.1	32.3	36	36.8	30.5
37.4	32.3	37	36.9	30.8
37.5	32.4	38	37.6	31.0
37.9	33.1	39	37.3	31.6
38.4	33.5	40	37.5	32.0
38.6	33.6	41	37.8	32.3
38.6	33.8	42	38.0	32.5
38.8	33.8	43	38.3	32.8
38.9	34.3	44	38.5	33.0
39.0	34.5	45	38.4	33.5
39.0	34.8	46	38.8	33.5
39.3	35.8	47	38.9	33.5
39.5	35.9	48	39.0	33.8

¹ From F. S. Quarterly Publication of the American Statistical Association, Boston, September, 1916, No. 115, pp. 532

HEIGHT—WEIGHT—AGE TABLE (BOYS)

Height Inches	5 Yrs	6 Yrs	7 Yrs	8 Yrs	9 Yrs	10 Yrs	11 Yrs	12 Yrs	13 Yrs	14 Yrs	15 Yrs	16 Yrs	17 Yrs	18 Yrs	19 Yrs
38	34	34													
39	35	35													
40	36	36													
41	38	38	38												
42	39	39	39	39											
43	41	41	41	41											
44	44	44	44	44											
45	46	46	46	46	46										
46	47	48	48	48	48										
47	49	50	50	50	50	50									
48		52	53	53	53	53									
49		55	55	55	55	55	55								
50		57	58	58	58	58	58	58							
51			61	61	61	61	61	61							
52			63	64	64	64	64	64	64						
53			66	67	67	67	67	68	68						
54				70	70	70	70	71	71	72					
55				72	72	73	73	74	74	74					
56				75	76	77	77	77	78	78	80				
57					79	80	81	81	82	83	83				
58					83	84	84	85	85	86	87				
59						87	88	89	89	90	90	90			
60						91	92	92	93	94	95	96			
61															
62															
63															
64															
65															
66															
67															
68															
69															
70										143	144	145	148	151	155
71										148	150	151	152	154	159
72											153	155	156	158	163
73											157	160	162	164	167
74											160	164	168	170	171

Prepared by Bird T Baldwin Ph D and Thomas D Wood M D

HEIGHT-WEIGHT-AGE TABLE GIRLS

Height, Inches	5 Yrs	6 Yrs	7 Yrs	8 Yrs	9 Yrs	10 Yrs	11 Yrs	12 Yrs	13 Yrs	14 Yrs	15 Yrs	16 Yrs	17 Yrs	18 Yrs
38	33	33												
39	34	34												
40	36	36	36											
41	37	37	37											
42	39	39	39											
43	41	41	41	41										
44	42	42	42	42										
45	45	45	45	43	43									
46	47	47	47	45	44									
47	49	50	50	50	50	50								
48		52	52	52	52	51	51							
49		54	54	55	53	50	50							
50		56	56	57	54	59	61	62						
51			59	60	61	61	61	63						
52			63	64	64	64	65	67						
53			66	67	67	68	68	69	71					
54				69	70	70	71	71	71					
55				72	74	74	74	75	77	78				
56					76	78	78	79	81	84				
57					80	82	82	82	84	88	91			
58						84	86	86	88	93	96	101		
59						87	90	90	92	96	100	101	104	
60						91	95	95	97	101	105	108	109	111
61							97	100	101	105	108	112	113	115
62							101	105	106	109	113	117	117	119
63								110	110	112	116	117	119	120
64								114	115	117	119	120	122	123
65									118	120	121	123	125	126
66										124	125	128	129	130
67										125	130	131	134	135
68										131	134	135	136	138
69											137	138	140	141
70											136	138	140	142
71											134	139	142	144

Prepared by Bird T. Baldwin, Ph.D., and Thomas D. Wood, M.D.

HEIGHT—WEIGHT—AGE TABLE (BOYS)

Height Inches	5 Yrs	6 Yrs	7 Yrs	8 Yrs	9 Yrs	10 Yrs	11 Yrs	12 Yrs	13 Yrs	14 Yrs	15 Yrs	16 Yrs	17 Yrs	18 Yrs	19 Yrs
38	34	34													
39	35	35													
40	36	36													
41	38	38	38												
42	39	39	39	39											
43	41	41	41	41											
44	41	41	41	41											
45	46	46	46	46	46										
46	47	48	48	48	48										
47	49	50	50	50	50	50									
48		52	53	53	53	53									
49		55	55	55	55	55	55								
50		57	58	58	58	58	58	58							
51			61	61	61	61	61	61							
52			63	64	64	64	64	64	64						
53			66	67	67	67	67	68	68						
54				70	70	70	70	71	71	72					
55				72	72	73	73	74	74	74					
56				75	76	77	77	77	78	78	80				
57					79	80	81	81	82	83	83				
58					83	84	84	85	85	86	87				
59						87	88	89	89	90	90	90			
60						91	92	92	93	94	95	96			
61															
62															
63															
64															
65															
66															
67															
68															
69															
70										133	144	145	148	151	155
71										148	150	151	152	154	159
72											153	155	156	158	163
73											157	160	162	164	167
74											160	164	168	170	171

Prepared by Bird T. Baldwin Ph D and Thomas D. Wood M D

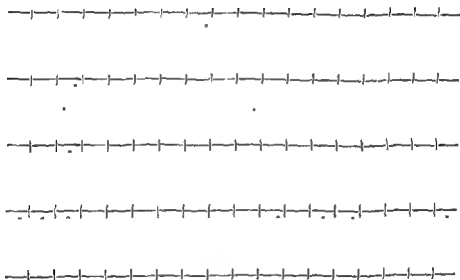
HEIGHT-WEIGHT-AGE TABLE (GIRLS)

Height Inches	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs	11 yrs	12 yrs	13 yrs	14 yrs	15 yrs	16 yrs	17 yrs	18 yrs
38	33	33												
39	34	34												
40	36	36	36											
41	37	37	37											
42	39	39	39											
43	41	41	41	41										
44	42	42	42	42										
45	45	45	45	45	45									
46	47	47	47	48	48									
47	49	50	50	50	50	50								
48		52	52	52	52	53	53							
49		54	54	55	55	56	56							
50		56	56	57	58	59	61	62						
51			59	60	61	61	63	65						
52			63	64	64	64	65	67						
53			66	67	67	68	68	69	71					
54				69	70	70	71	71	73					
55				72	74	74	74	75	77	78				
56					76	78	78	79	81	83				
57					80	82	82	82	84	84	92			
58						84	86	86	88	93	96	101		
59						87	90	90	92	96	100	101	104	
60						91	95	95	97	101	105	108	109	111
61							97	100	101	105	108	112	113	116
62							104	105	106	109	113	115	117	118
63								110	110	112	116	117	119	120
64								114	115	117	119	120	122	123
65								118	120	121	122	123	125	126
66									124	124	125	128	129	130
67									125	130	131	133	133	135
68									131	133	135	136	138	138
69										135	137	138	140	142
70										136	138	140	142	144
71										138	140	142	144	145

Prepared by Edward T. Baldwin Ph D and Thomas H. Wood M D

HEIGHTS AND WEIGHTS OF 136,504 WOMEN FIFTEEN OR MORE YEARS OF AGE (WITH CLOTHES)¹

Age	Graded average Weight in Pounds with Clothes																
	Feet and Inches with Shoes																
	4-8	4-9	4-10	4-11	5-0	5-1	5-2	5-3	5-4	5-5	5-6	5-7	5-8	5-9	5-10	5-11	6-0



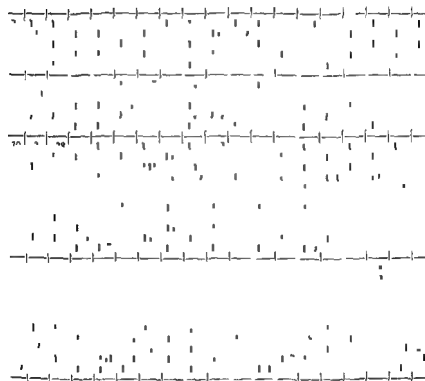
55	125	127	129	131	133	135	138	141	144	148	153	158	163	167	172	174	177
----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

¹ Association of Life Insurance Directors and Actuarial Society of America New York, 1912

p 67 Published by a committee Allow 1½ inches for shoes and 6 pounds for clothes

HEIGHTS AND WEIGHTS OF 221 819 MEN FIFTEEN OR MORE YEARS OF AGE (WITH CLOTHES)

Age	Graded Average Weight in Pounds with Clothes															
	Feet and Inches with Shoes															
	5-0	5-1	5-2	5-3	5-4	5-5	5-6	5-7	5-8	5-9	5-10	5-11	6-0	6-1	6-2	6-3



55	135	137	139	142	145	149	153	158	163	168	173	178	184	191	198	205	212	218
----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

¹ Association of Life Insurance Directors and Actuarial Society of America, New York, 1910.
 238 Published by a committee. Allow 1 inch for shoes and 10 pounds for clothes.

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